



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 179313

TO: David Lukton
Location: REM/3B75/3C18
Art Unit: 1654
February 28, 2006

Case Serial Number: 10/600303

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

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SEARCH REQUEST FORM
(STIC)

Requestor's Name: David Lukton

Examiner number: 71263

Date:

2/10/06

Art Unit: 1654

Phone number: 571-272-0952

Serial Number:

10-600303

Mail Box: 3-C-18

Examiner Rm: 3-B-75

Results format: paper

Title: CYCLOSPORIN DERIVATIVES FOR THE TREATMENT OF IMMUNE DISORDERS

Applicants: WU, FRANK X. H.; OR, YAT SUN

Earliest Priority Date: 6/20/03

Applicants are claiming the cyclosporin analogs on the attached sheet. (The claimed compounds differ from the prior art primarily in variable R_i)

R₂ = anything;

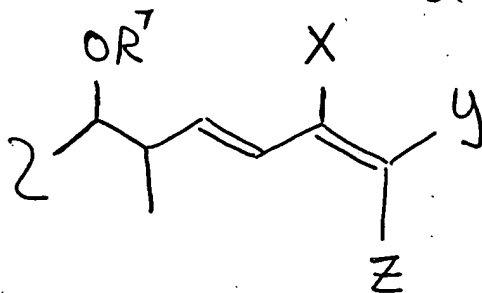
R₃ = isobutyl;

R₄ = anything;

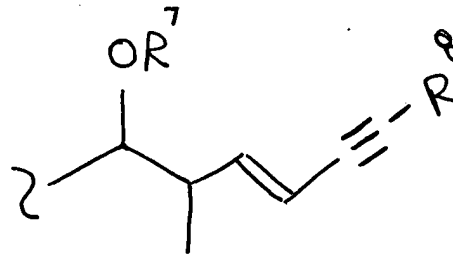
R₅ = isobutyl;

R₆ = isobutyl;

R₁ is either of the following (variables R₇, R₈, X, Y and Z can be anything):

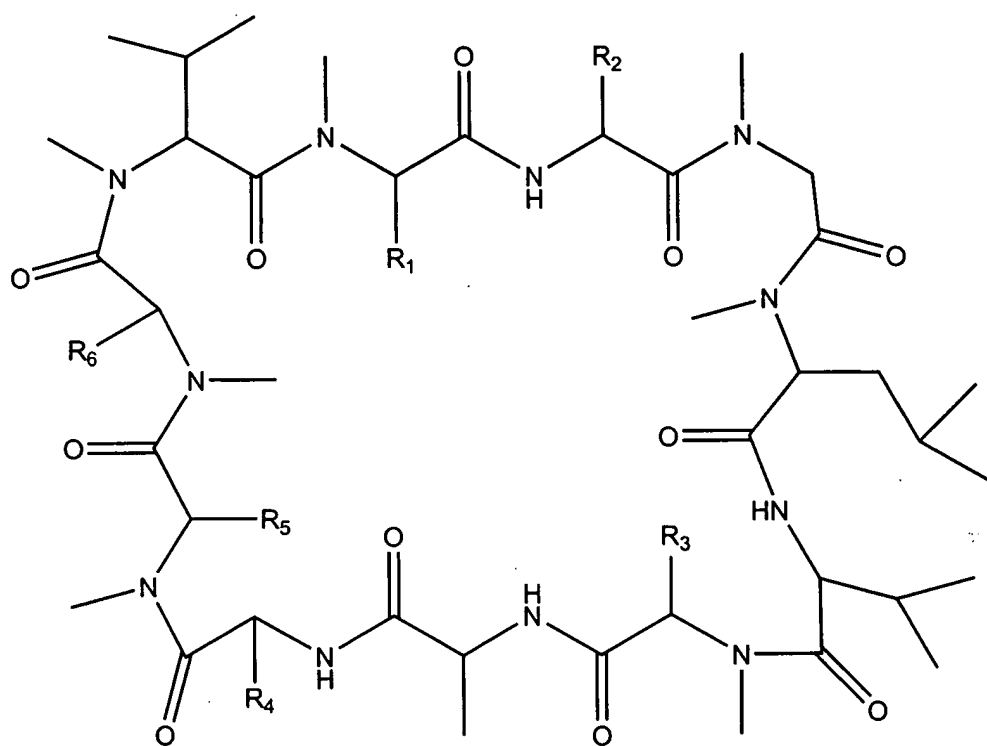


or



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10/600303



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Lukton 10_600303- - History

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(FILE 'REGISTRY' ENTERED AT 17:30:30 ON 28 FEB 2006)

L3 STR
L5 1743 SEA SSS FUL L3
L6 STR
L7 53 SEA SUB=L5 SSS FUL L6

FILE 'HCAPLUS' ENTERED AT 17:40:10 ON 28 FEB 2006

L8 2 SEA ABB=ON PLU=ON L7
D STAT QUE
D IBIB ABS HITSTR L8 1-2
L9 42 SEA ABB=ON PLU=ON "WU FRANK"/AU OR "WU FRANK X H"/AU
L10 216 SEA ABB=ON PLU=ON "WU F"/AU OR "WU F X"/AU
E OR Y/AU
L11 164 SEA ABB=ON PLU=ON "OR Y S"/AU OR ("OR YAT S"/AU OR "OR YAT
SU"/AU OR "OR YAT SUN"/AU OR "OR YATSUN"/AU)
L12 41 SEA ABB=ON PLU=ON L9 NOT L8
D STAT QUE L12
D IBIB ABS L12 1-41
L13 0 SEA ABB=ON PLU=ON (L10 AND L11) NOT (L8 OR L12)
D STAT QUE L13

FILE 'REGISTRY' ENTERED AT 17:48:02 ON 28 FEB 2006

L14 1690 SEA ABB=ON PLU=ON L5 NOT L7

FILE 'HCAPLUS' ENTERED AT 17:48:06 ON 28 FEB 2006

L15 15837 SEA ABB=ON PLU=ON L14
L16 22483 SEA ABB=ON PLU=ON L15 OR CYCLOSPOR?
L17 13 SEA ABB=ON PLU=ON (L16 AND (L10 OR L11)) NOT (L8 OR L12)
D STAT QUE NOS
D IBIB ABS HITSTR L17 1-13

FILE HCAPLUS

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FILE COVERS 1907 - 28 Feb 2006 VOL 144 ISS 10

FILE LAST UPDATED: 27 Feb 2006 (20060227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 FEB 2006 HIGHEST RN 875402-35-0

DICTIONARY FILE UPDATES: 27 FEB 2006 HIGHEST RN 875402-35-0

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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conducting SmartSELECT searches.

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*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005. A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*
*****
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Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
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experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

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FILE 'HCAPLUS' ENTERED AT 17:40:10 ON 28 FEB 2006

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FILE COVERS 1907 - 28 Feb 2006 VOL 144 ISS 10

FILE LAST UPDATED: 27 Feb 2006 (20060227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

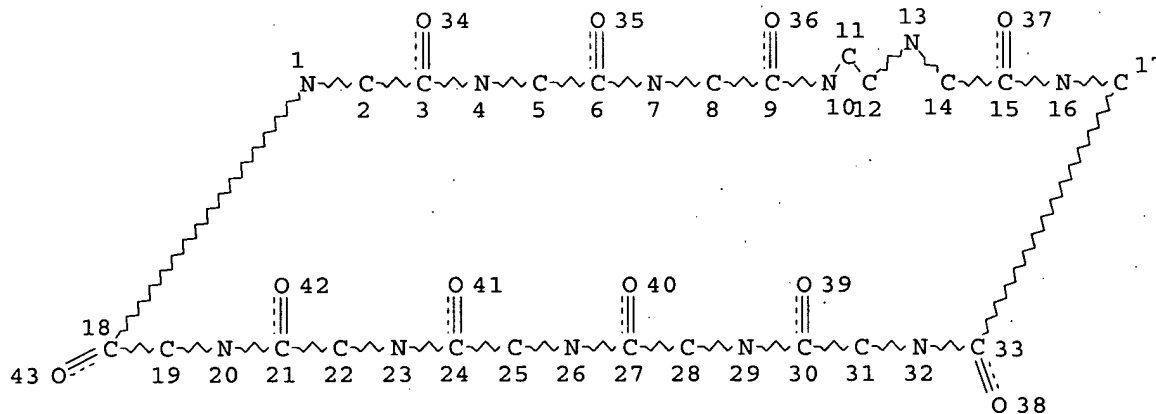
This file contains CAS Registry Numbers for easy and accurate substance identification.

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L3 STR



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DEFAULT ECLEVEL IS LIMITED

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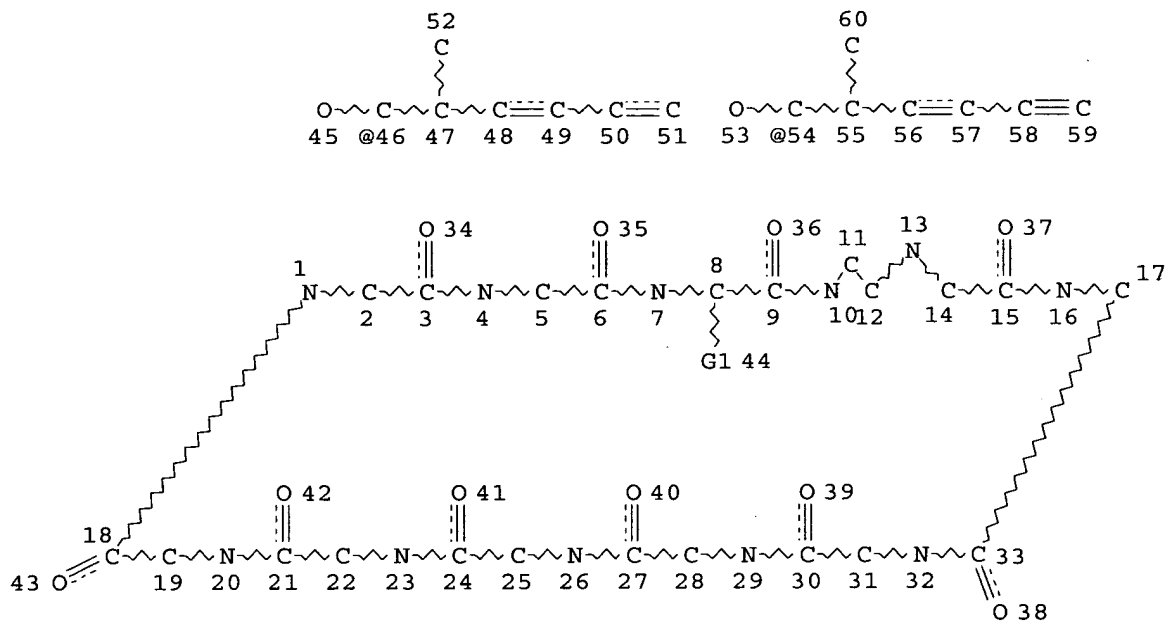
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NUMBER OF NODES IS 43

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L6 STR



VAR G1=46/54

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$$\Rightarrow$$
$$= \gamma$$

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L8 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:2159 HCAPLUS

DOCUMENT NUMBER: 142:74845

TITLE: Preparation of cyclosporin derivatives for the treatment of immune disorders

INVENTOR(S) : Wu, Frank X. H.; Or, Yat Sun

PATENT ASSIGNEE (S) : USA

SOURCE: U.S. Pat. Appl. Publ., 34 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

KIND

APPLICATION NO.

DATE _____

US 2004266669 A1 20041230 US 2003-600303 20030620
 WO 2005000879 A1 20050106 WO 2004-US15805 20040519

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
 CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
 SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
 SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-600303 A 20030620

OTHER SOURCE(S): MARPAT 142:74845

AB The invention relates to cyclosporin analogs cyclo[NMeCH(A)CO-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is CH(OW)CHMeCH:CH-Q (stereo not shown), where Q is an ethylenic or acetylenic group of defined structure and W is H or a protecting group; B is α Abu, Val, Thr or Nva; U is D-Ala, D-Ser, O-(2-hydroxyethyl)-, O-acyl- or O-(2-acyloxyethyl)-D-Ser] or a prodrug or pharmaceutically-acceptable salt for treating autoimmune diseases or for the prevention of organ transplantation rejection in a subject. Thus, the side chain (A) of cyclosporin A [I; A = CH(OH)CMeCH₂CH:CHMe, B = α Abu, U = D-Ala] was modified by acetylation, oxidation to the aldehyde, reaction with vinylmagnesium bromide, acetylation, and elimination reaction using Pd(OAc)₂/Ph₃P to afford I [A = CH(OAc)CHMeCH:CHCH:CH₂, B = α Abu, U = D-Ala].

IT 813426-55-0P 813426-56-1P 813426-57-2P
 813426-58-3P 813426-59-4P 813426-60-7P
 813426-61-8P 813426-62-9P 813426-63-0P
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 813426-79-8P 813426-80-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of cyclosporin derivs. for treatment of immune disorders)

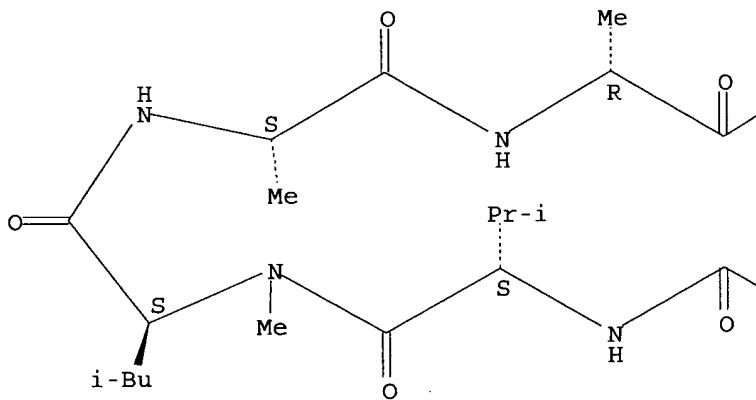
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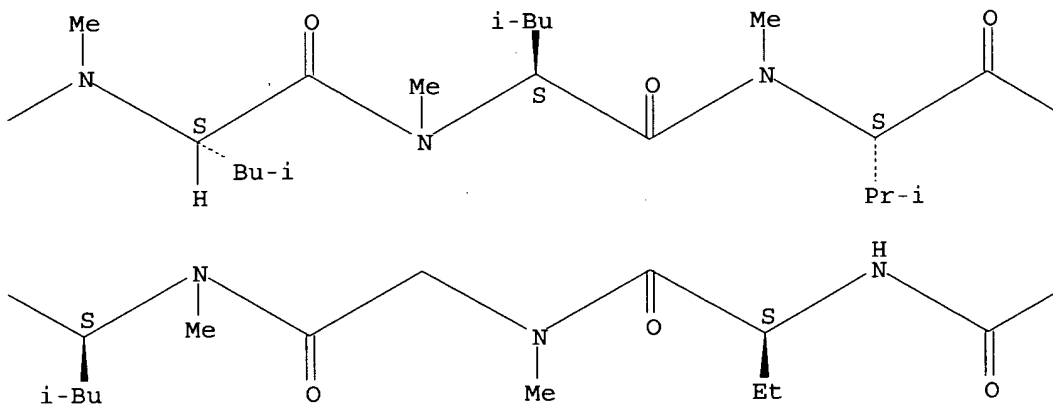
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Double bond geometry unknown.

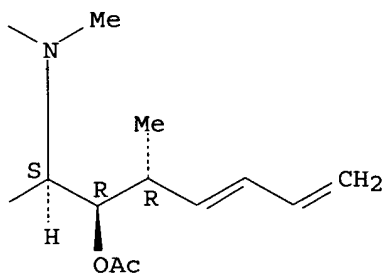
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PAGE 1-B



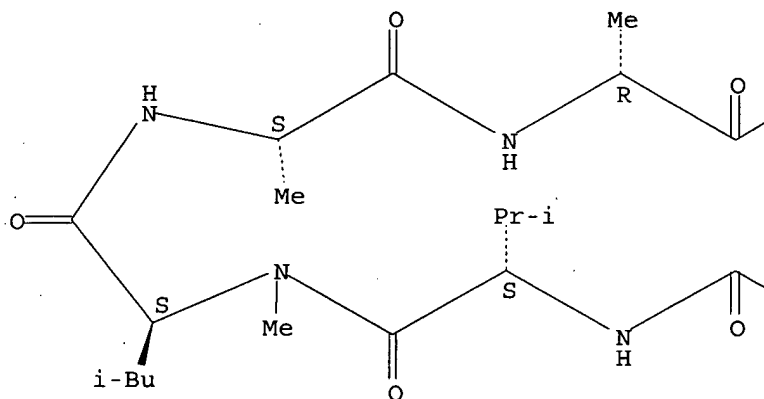
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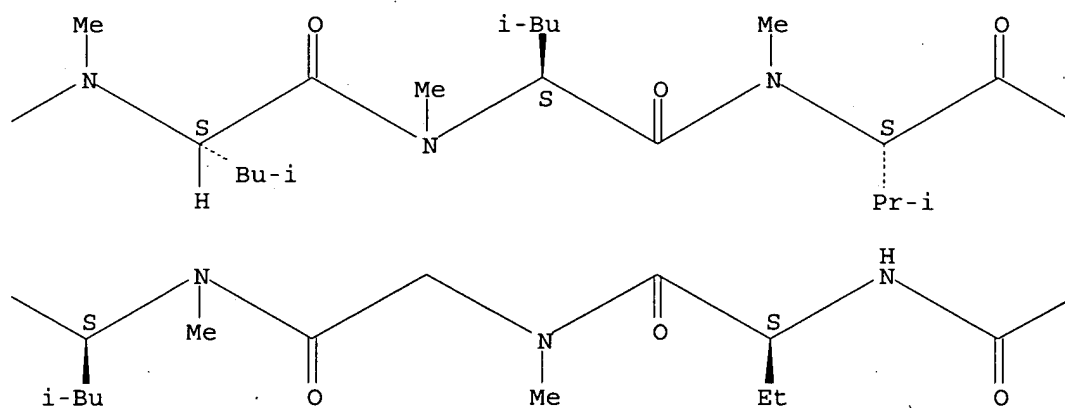
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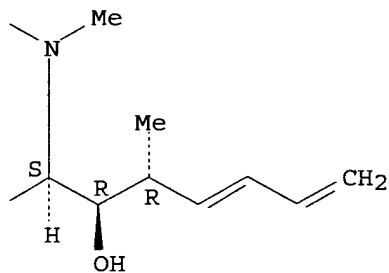
Absolute stereochemistry.
Double bond geometry unknown.

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PAGE 1-B



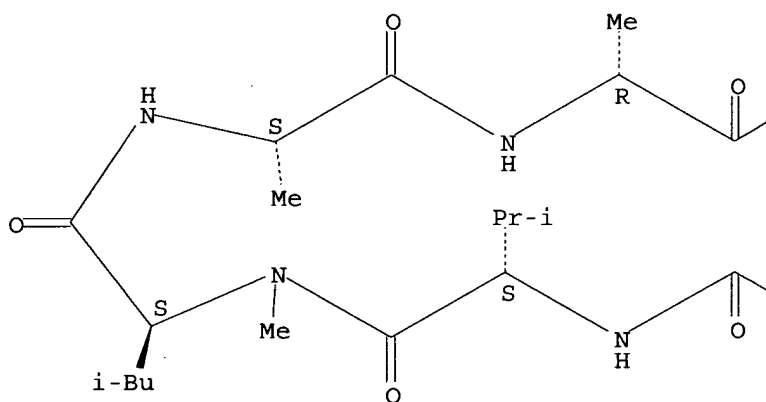


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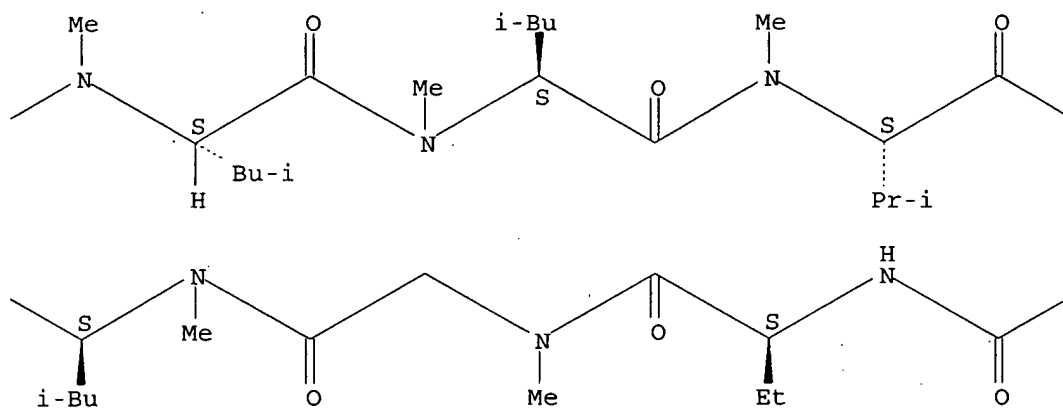
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Absolute stereochemistry.

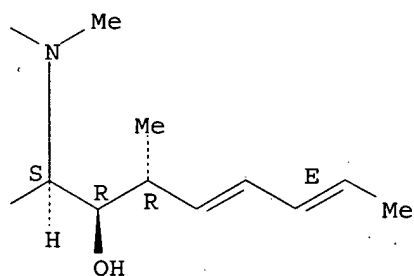
Double bond geometry as described by E or Z.



PAGE 1-B



PAGE 1-C



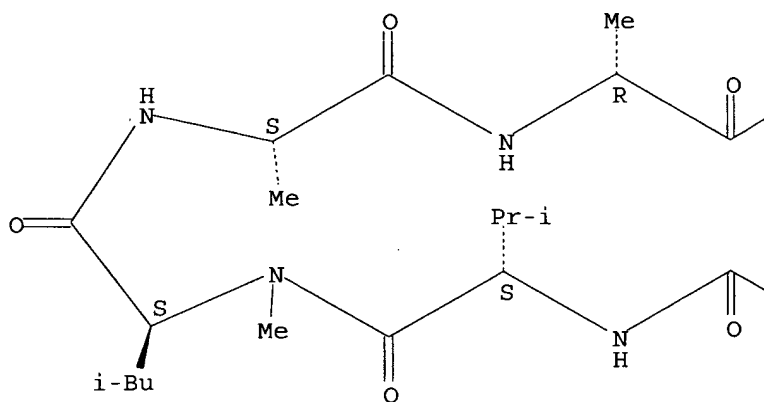
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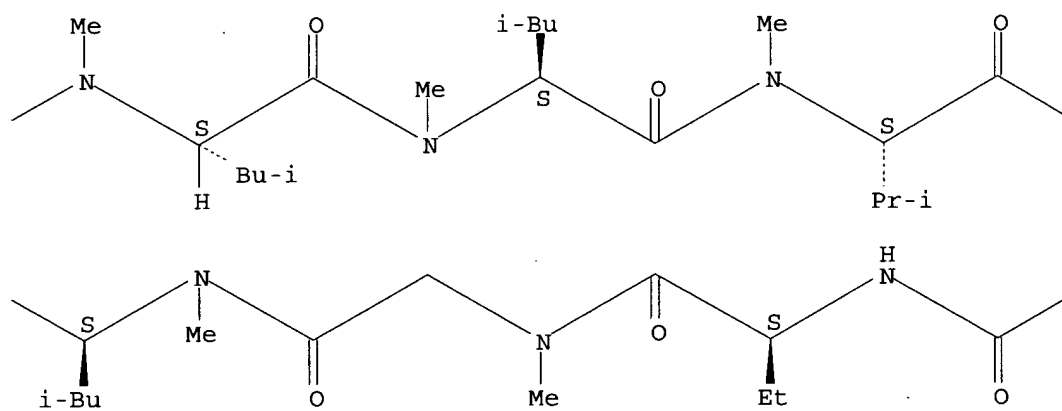
Absolute stereochemistry.

Double bond geometry unknown.

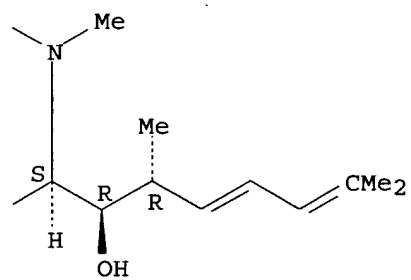
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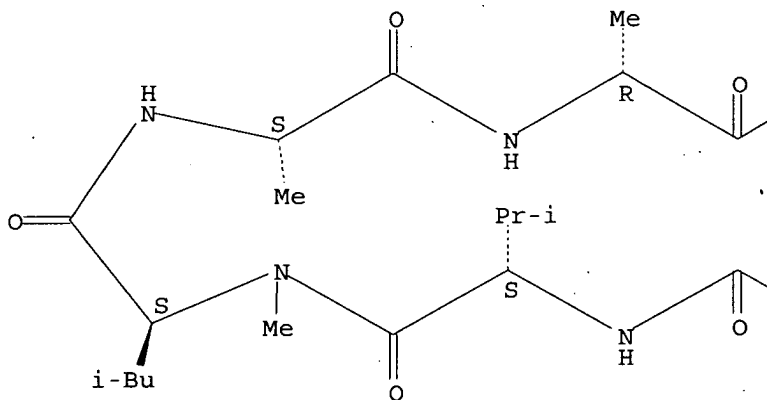
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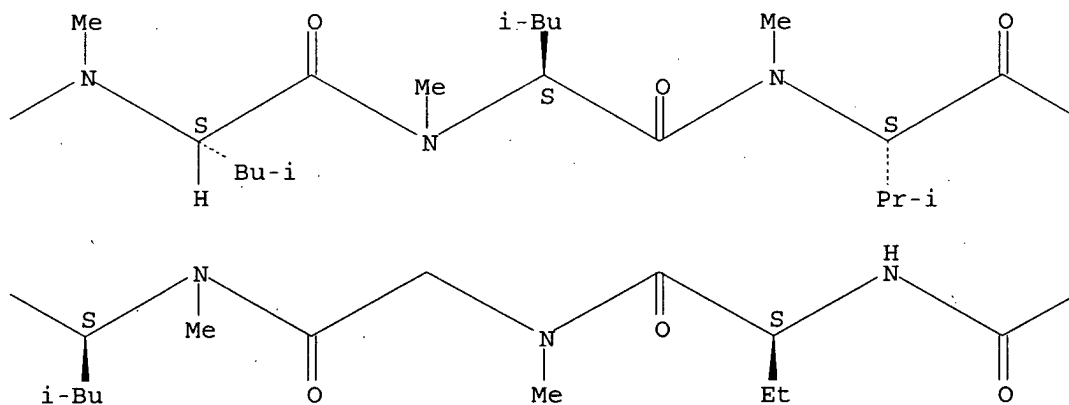
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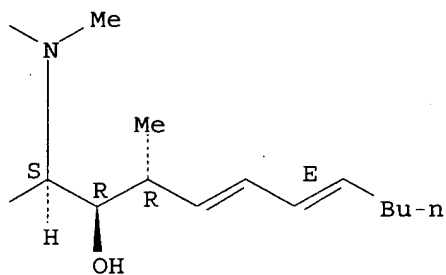
Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B



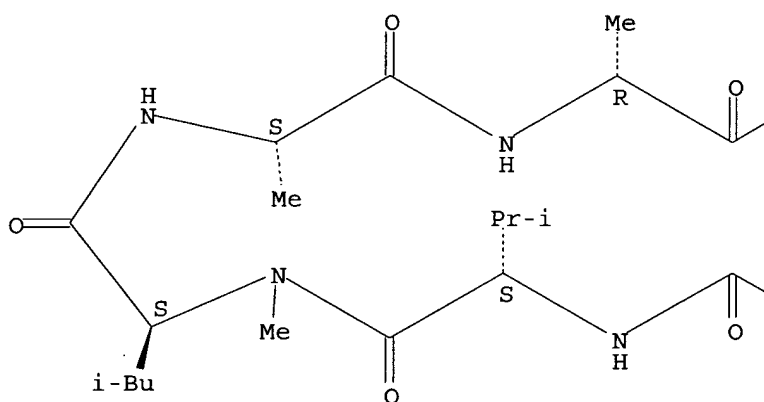


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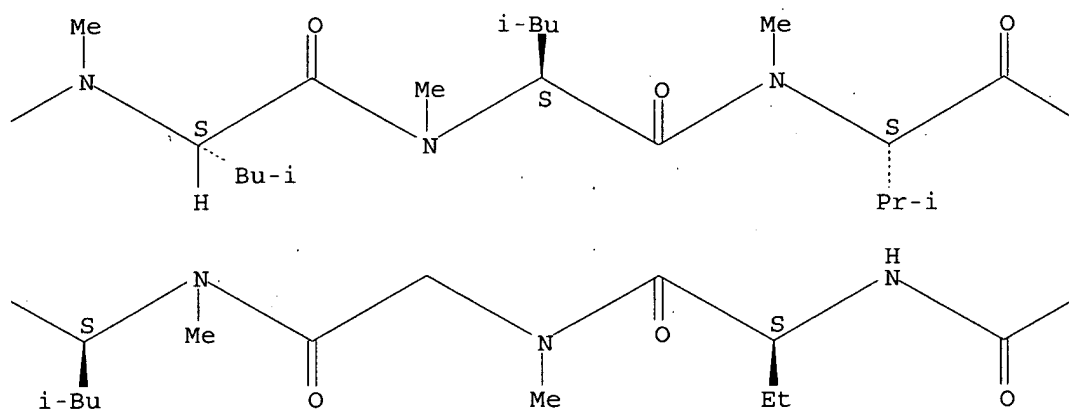
CN Cyclosporin A, 6-[(2S,3R,4R,7E)-10-bromo-3-hydroxy-4-methyl-2-(methylamino)-5,7-decadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

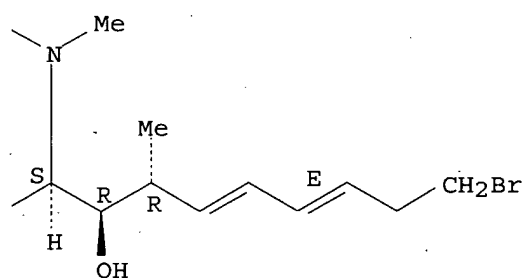
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PAGE 1-B



PAGE 1-C



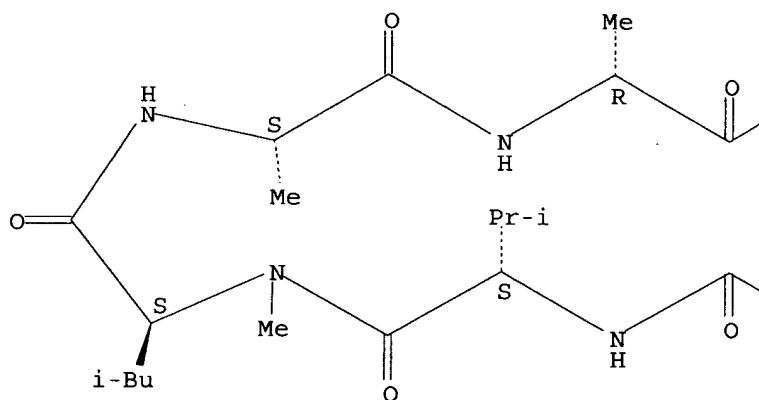
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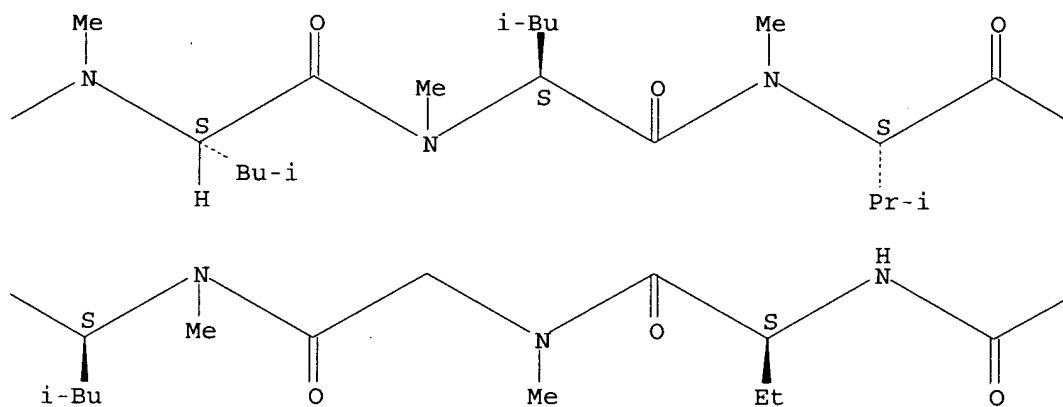
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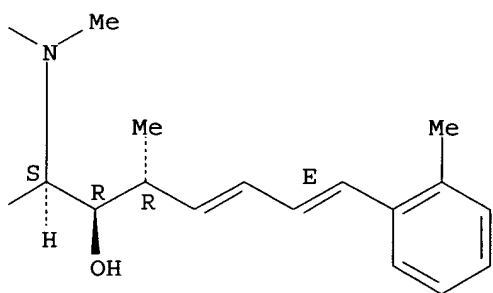
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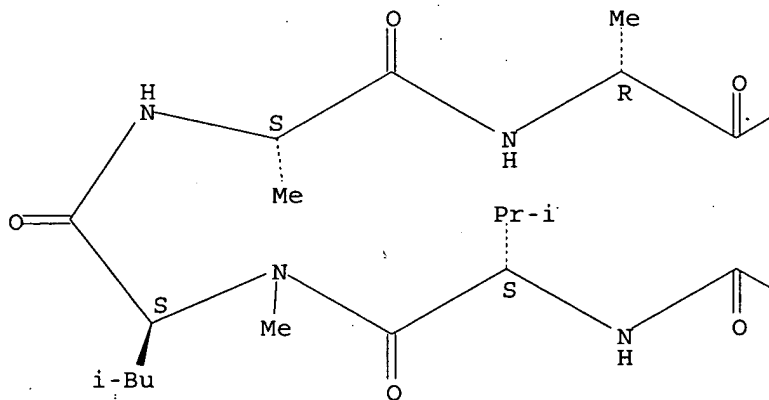
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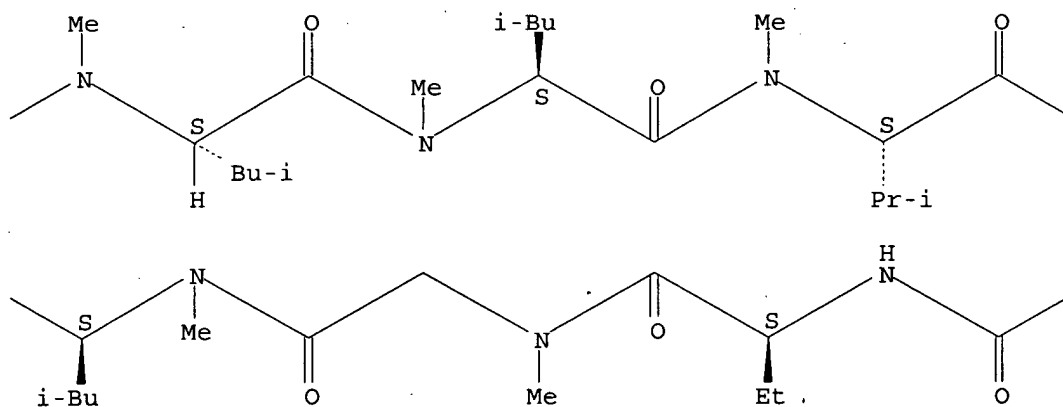
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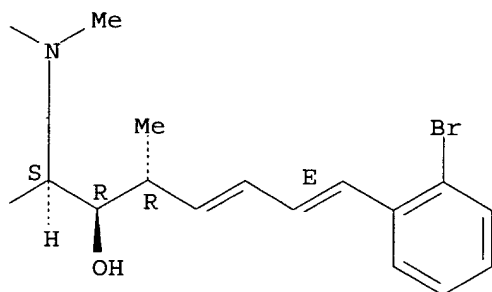
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PAGE 1-A



PAGE 1-B



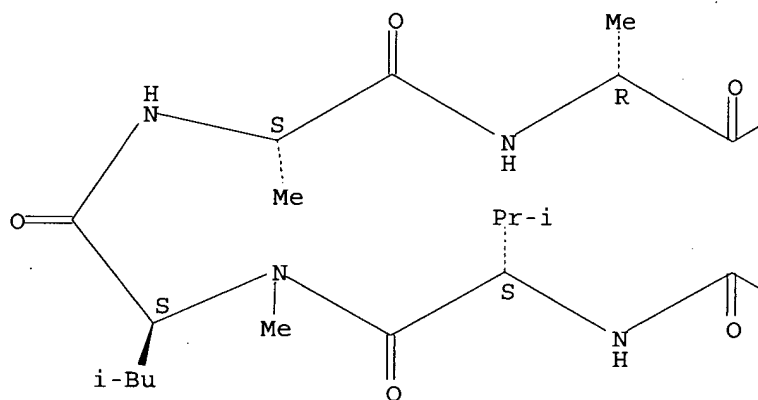


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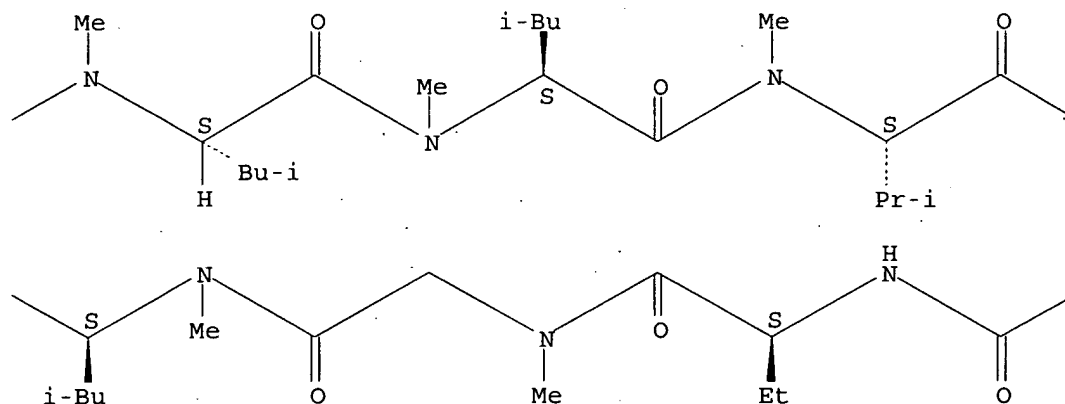
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Absolute stereochemistry.

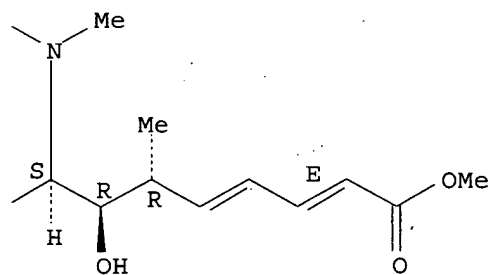
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PAGE 1-B



PAGE 1-C



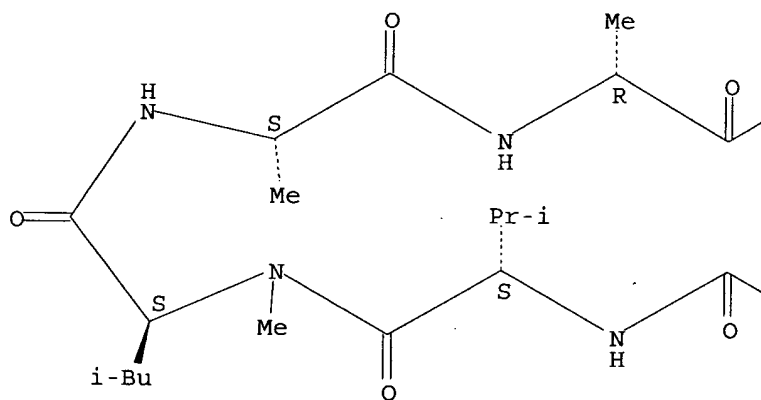
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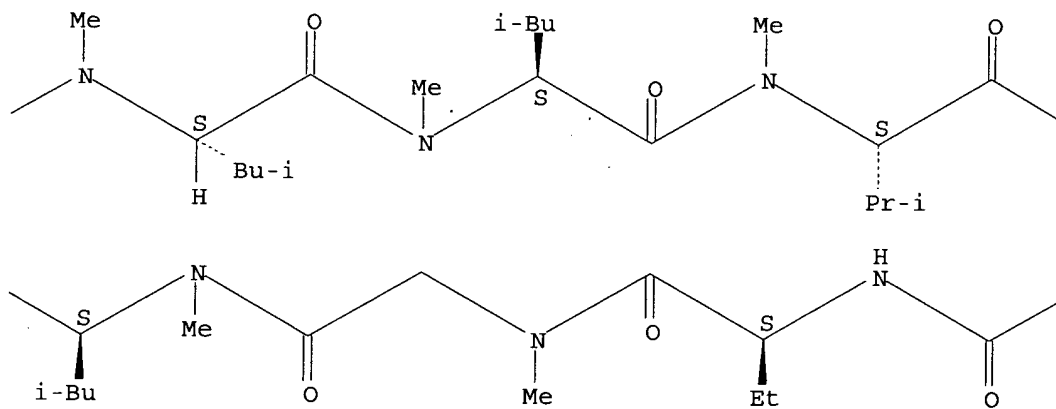
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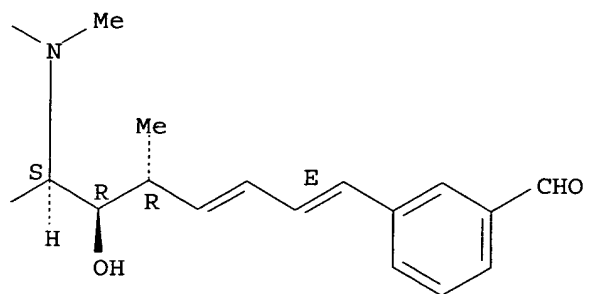
PAGE 1-A



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PAGE 1-C



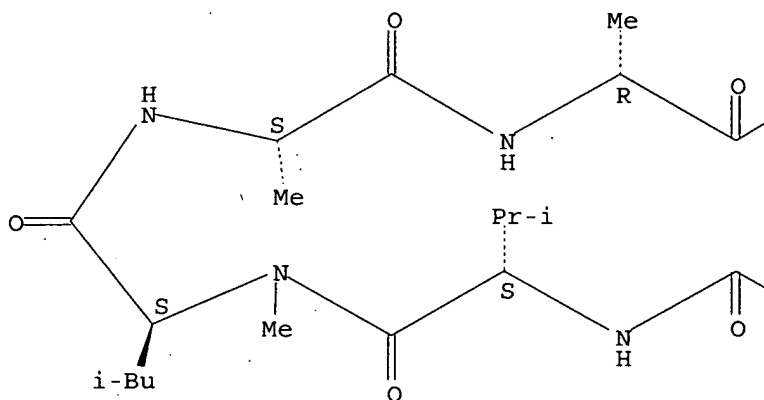
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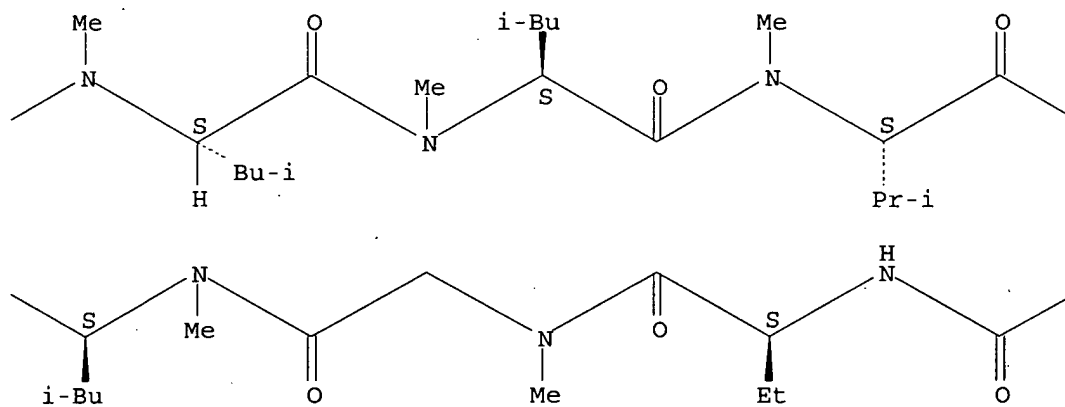
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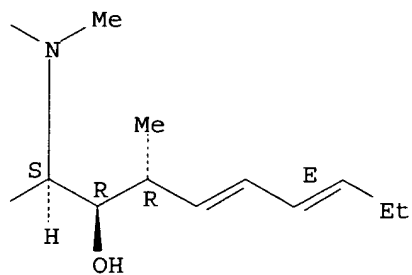
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PAGE 1-A



PAGE 1-B



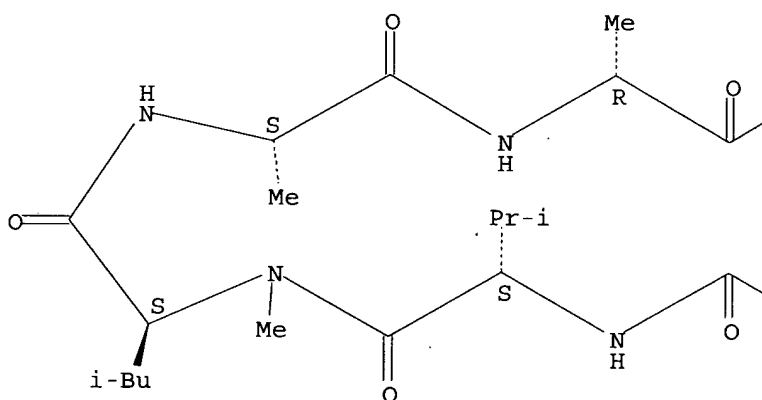


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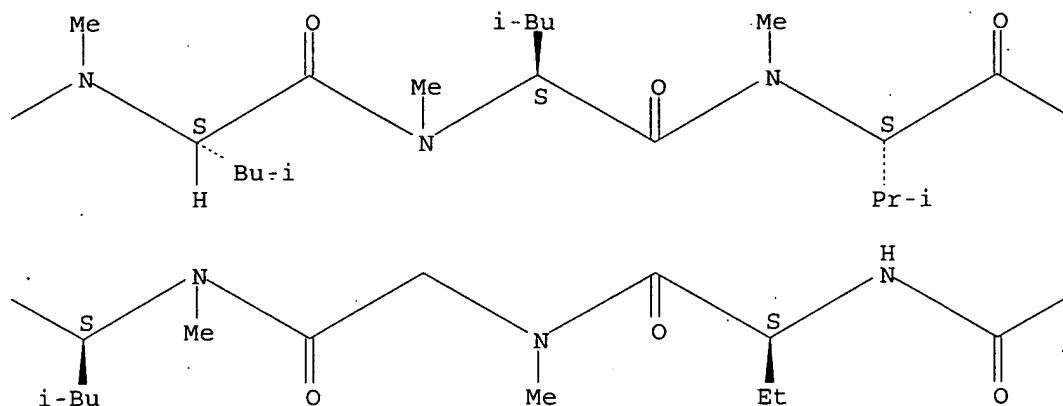
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Absolute stereochemistry.

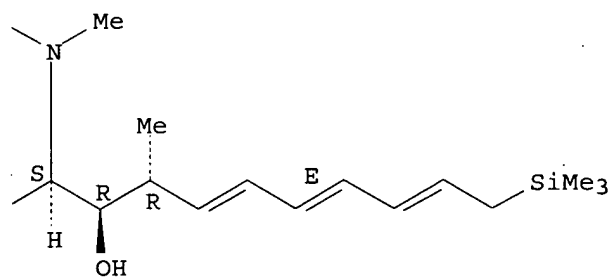
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PAGE 1-B



PAGE 1-C

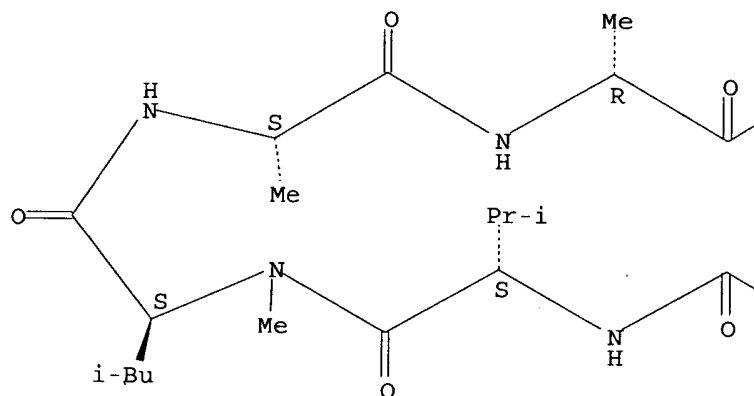


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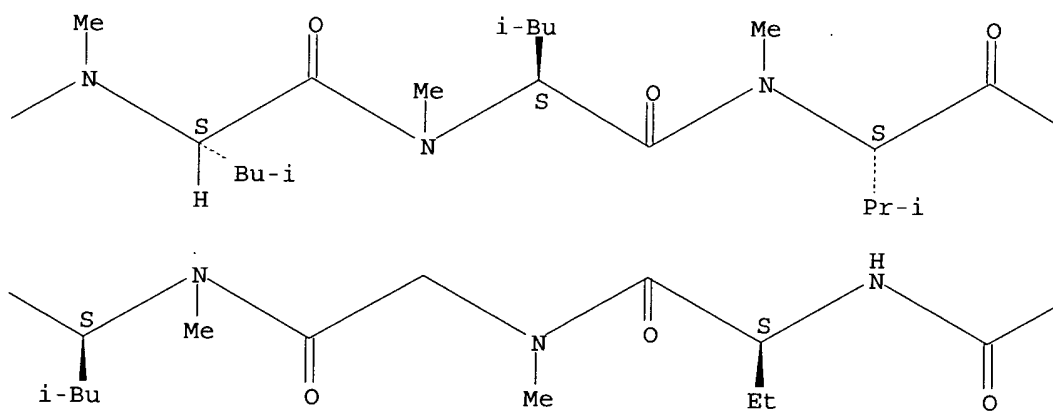
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Absolute stereochemistry.
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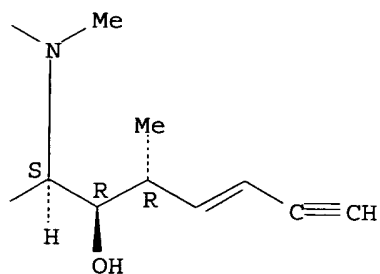
PAGE 1-A



PAGE 1-B



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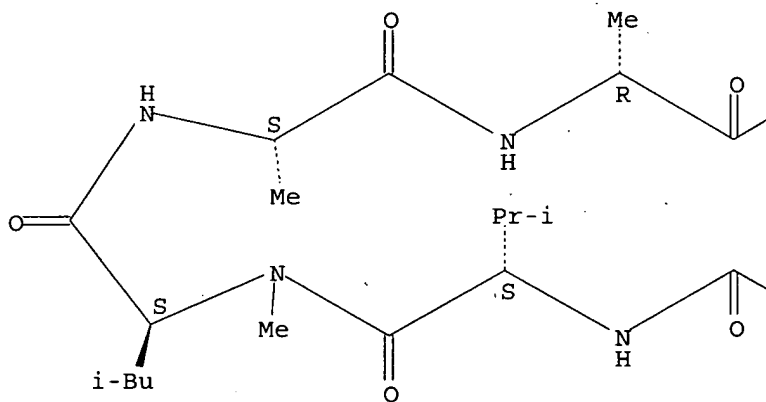
RN 813426-68-5 HCAPLUS

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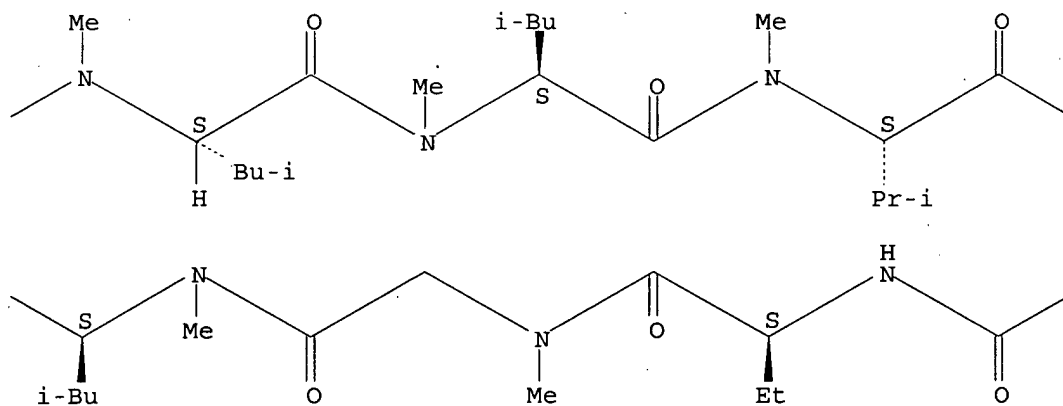
Absolute stereochemistry.

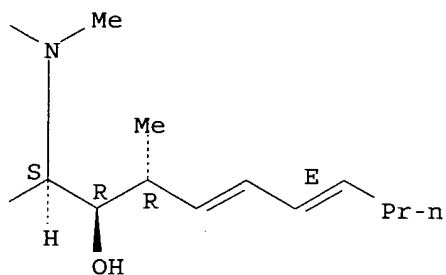
Double bond geometry as described by E or Z.

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PAGE 1-B



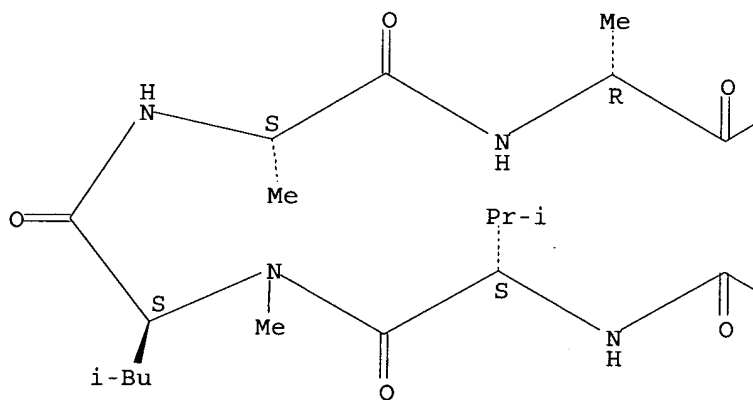


RN 813426-69-6 HCAPLUS

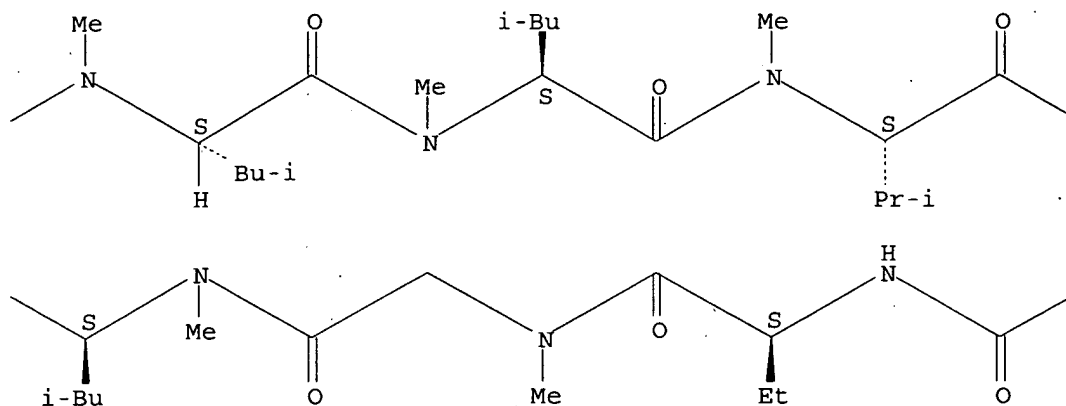
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Absolute stereochemistry.

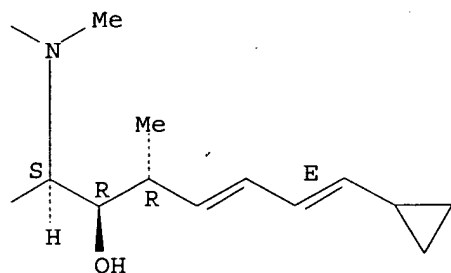
Double bond geometry as described by E or Z.



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PAGE 1-C



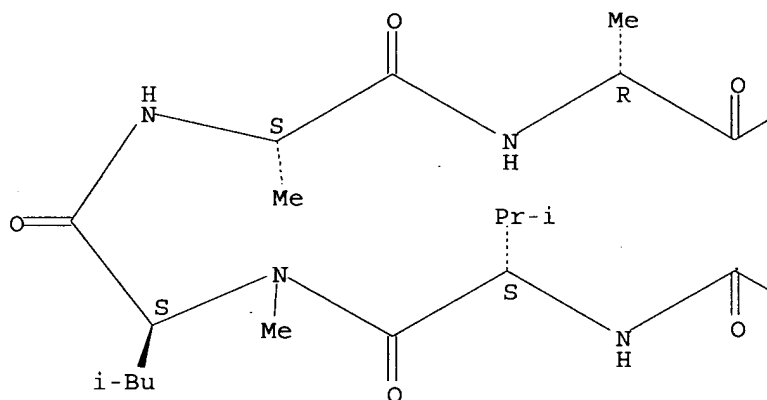
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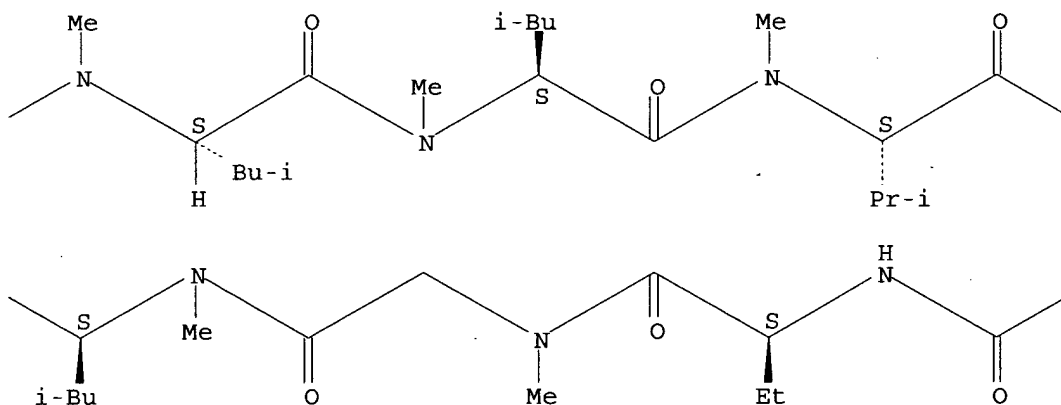
Absolute stereochemistry.

Double bond geometry as described by E or Z.

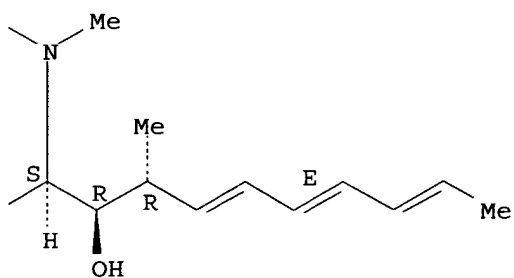
PAGE 1-A



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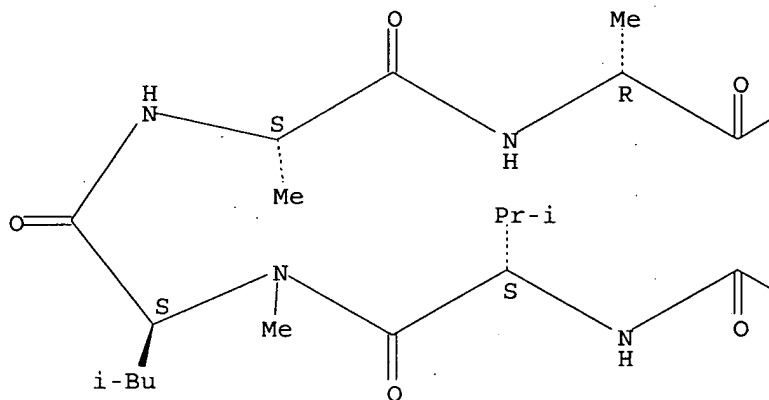
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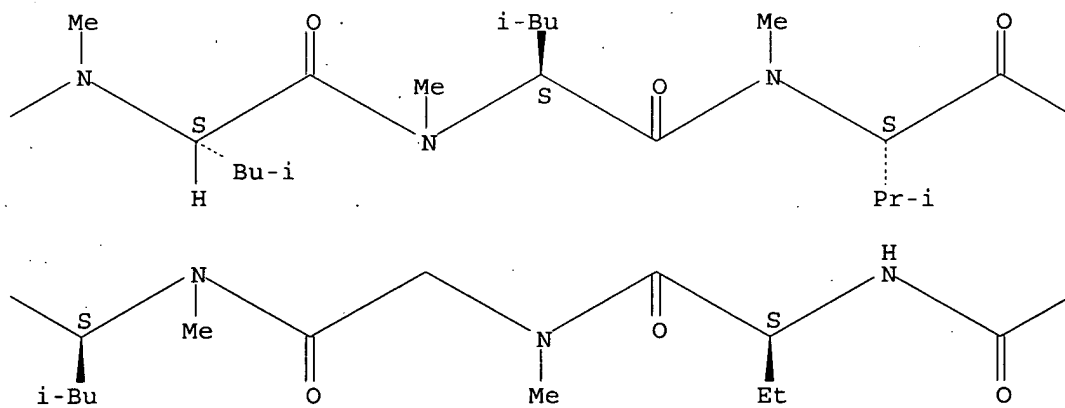
Absolute stereochemistry.

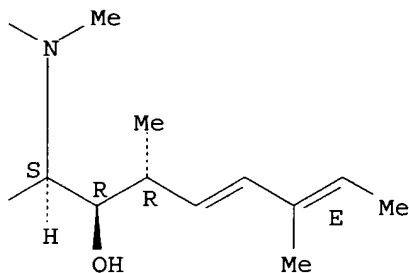
Double bond geometry as described by E or Z.

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PAGE 1-B



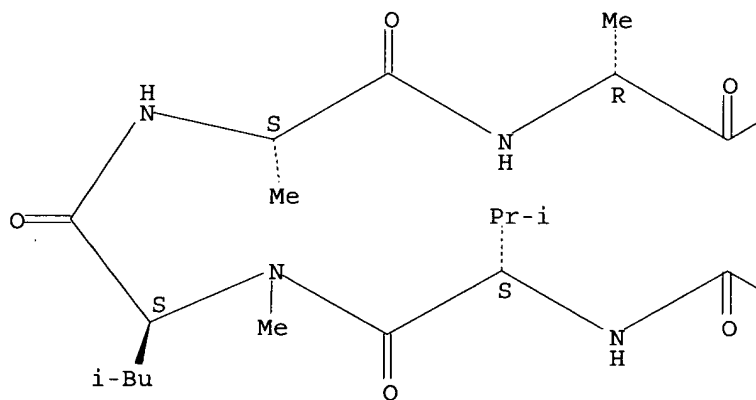


RN 813426-72-1 HCAPLUS

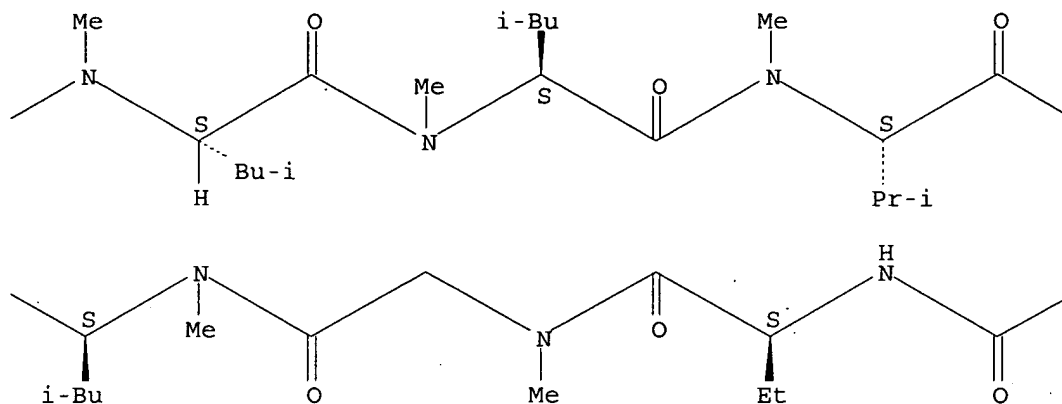
CN Cyclosporin A, 6-[(2S,3R,4R,7Z)-3-hydroxy-4-methyl-2-(methylamino)-5,7-nonadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

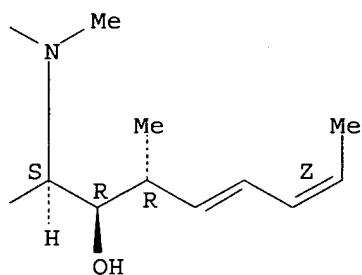
Double bond geometry as described by E or Z.



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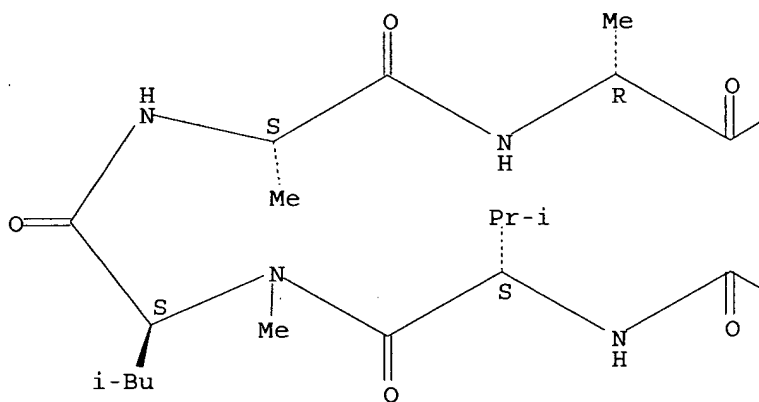
RN 813426-73-2 HCAPLUS

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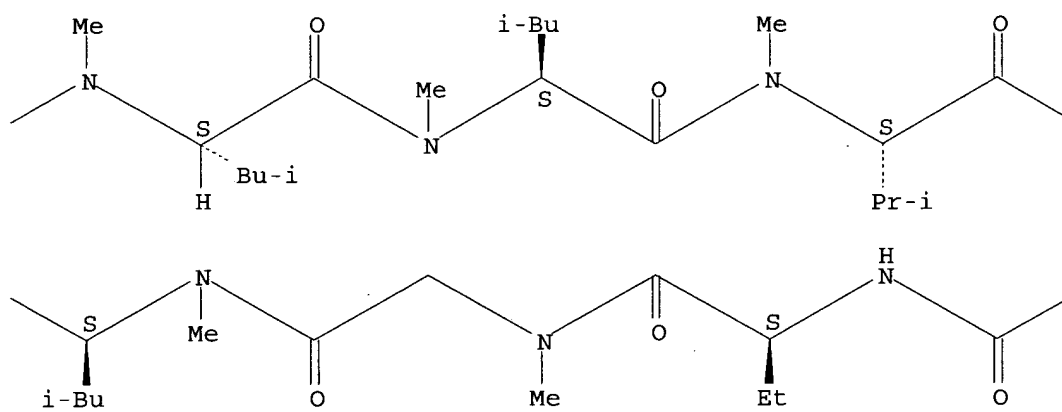
Absolute stereochemistry.

Double bond geometry as described by E or Z.

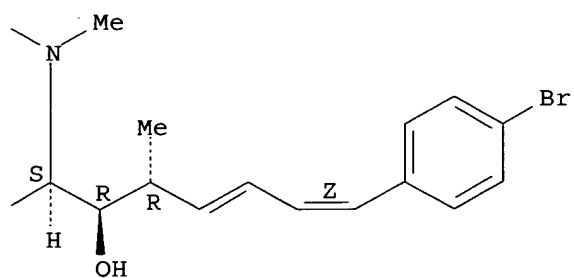
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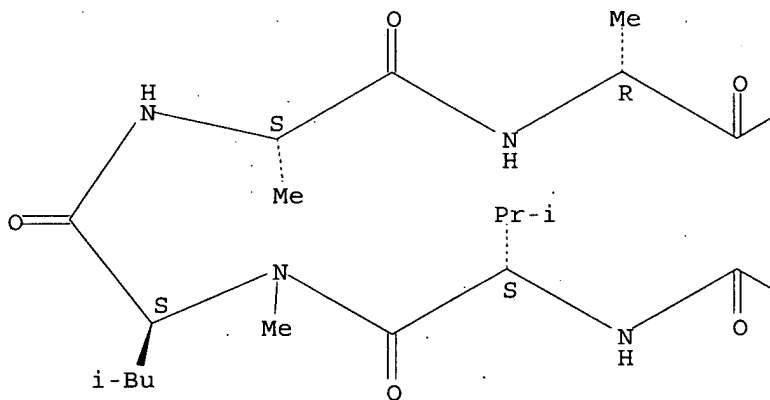
RN 813426-74-3 HCAPLUS

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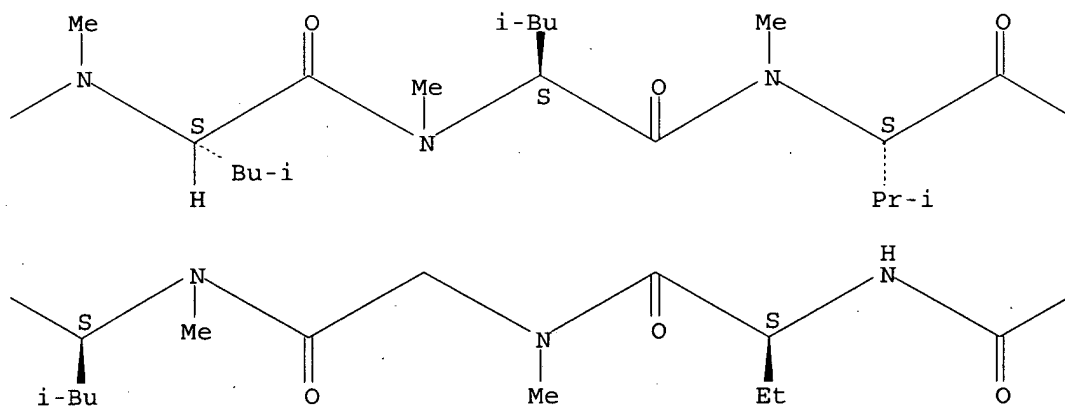
Absolute stereochemistry.

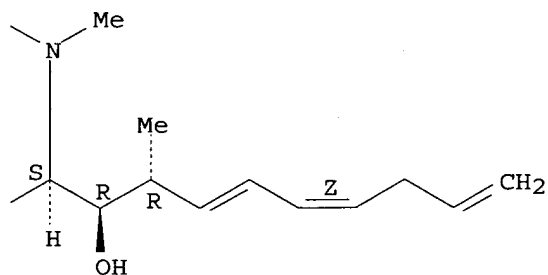
Double bond geometry as described by E or Z.

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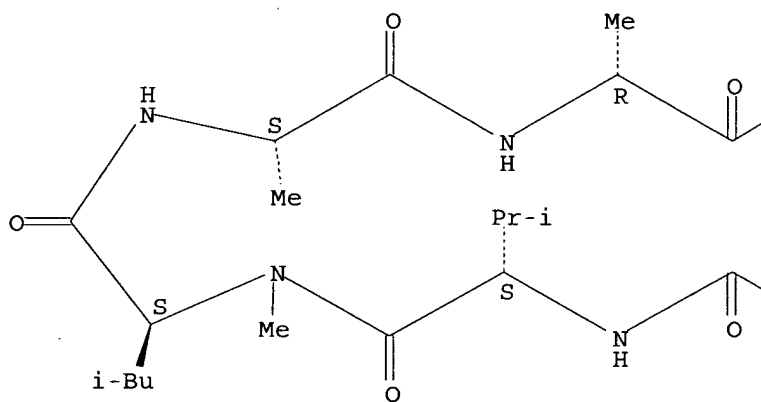


RN 813426-75-4 HCAPLUS

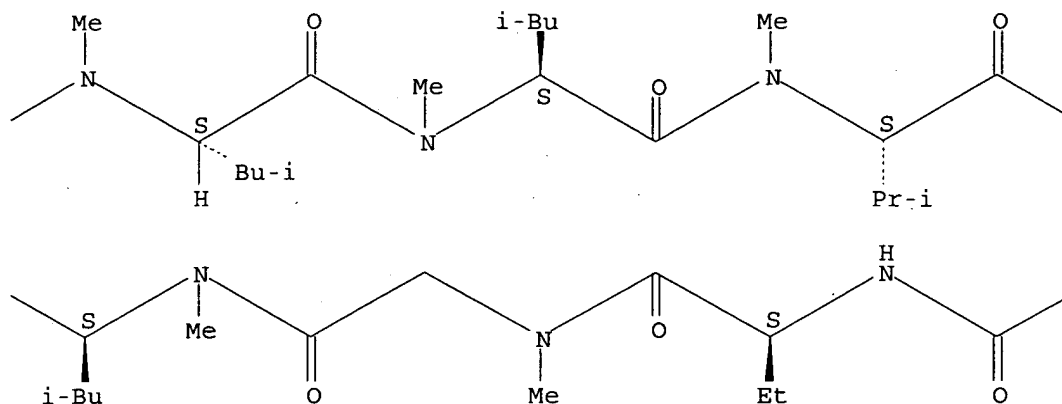
CN Cyclosporin A, 6-[(2S,3R,4R,7Z)-3-hydroxy-4-methyl-2-(methylamino)-5,7-decadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

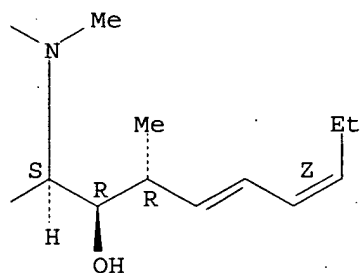
Double bond geometry as described by E or Z.



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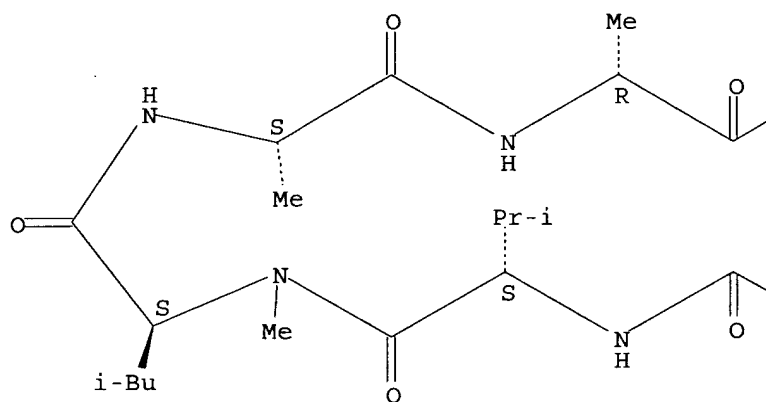
RN 813426-76-5 HCAPLUS

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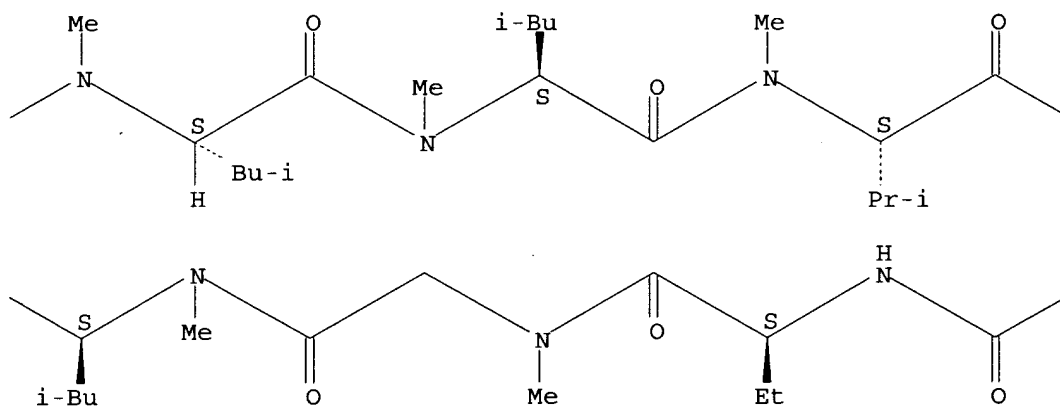
Absolute stereochemistry.

Double bond geometry as described by E or Z.

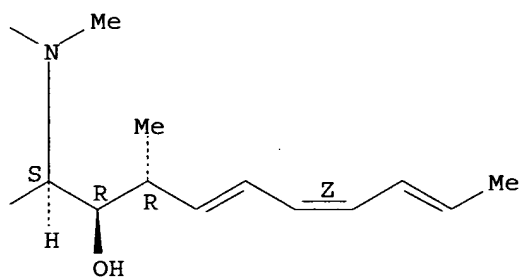
PAGE 1-A



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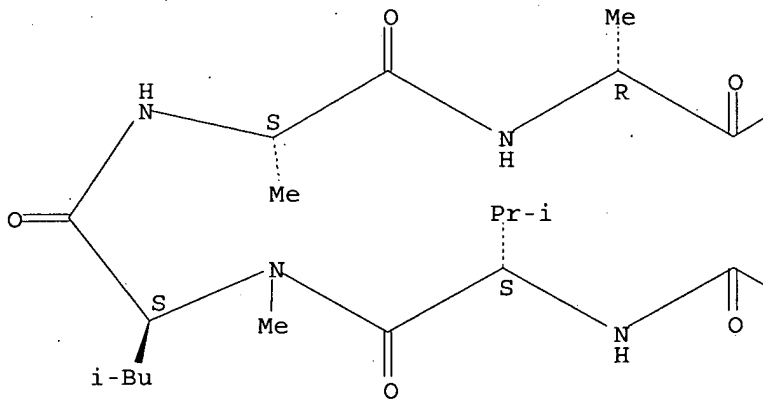
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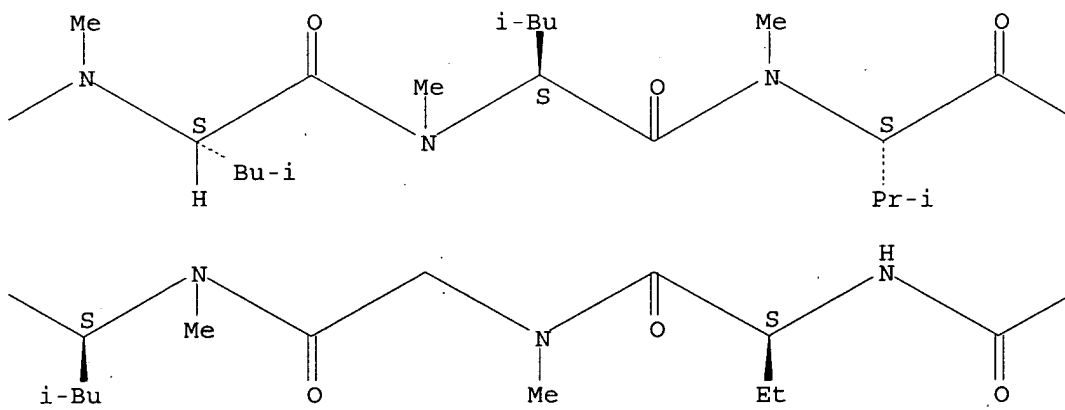
Absolute stereochemistry.

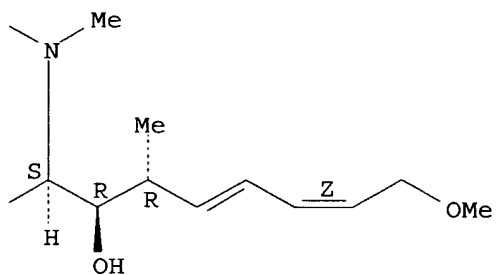
Double bond geometry as described by E or Z.

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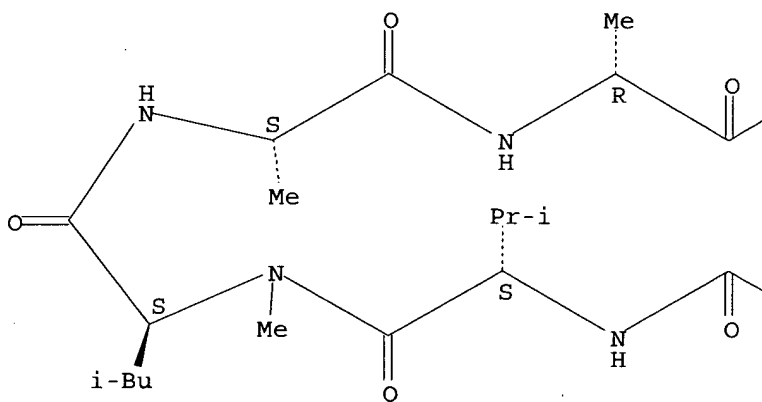




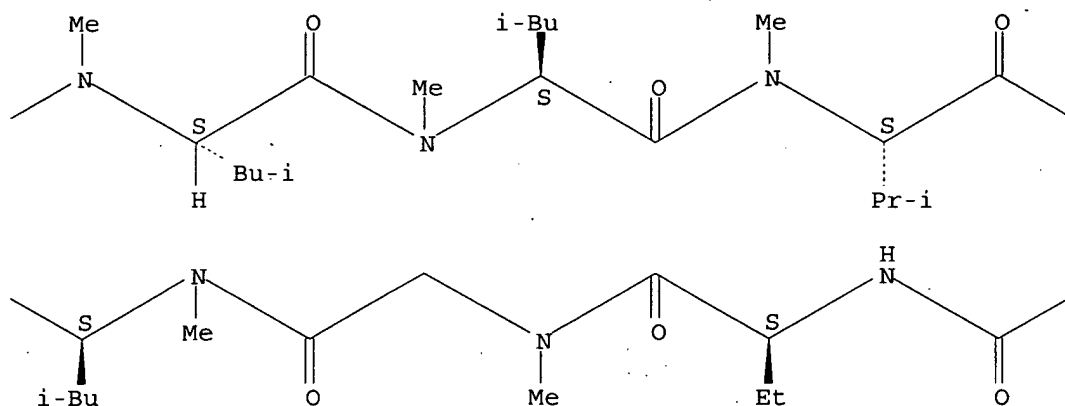
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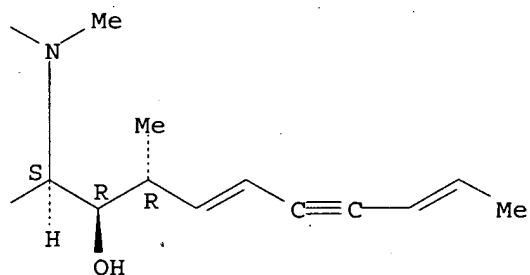
Absolute stereochemistry.
Double bond geometry unknown.



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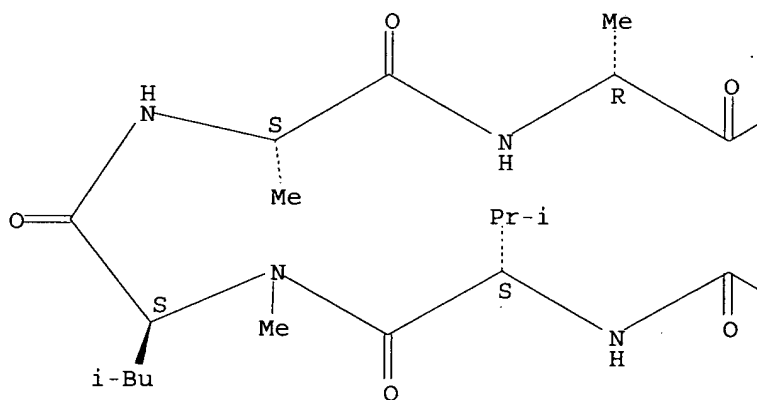


RN 813426-79-8 HCAPLUS

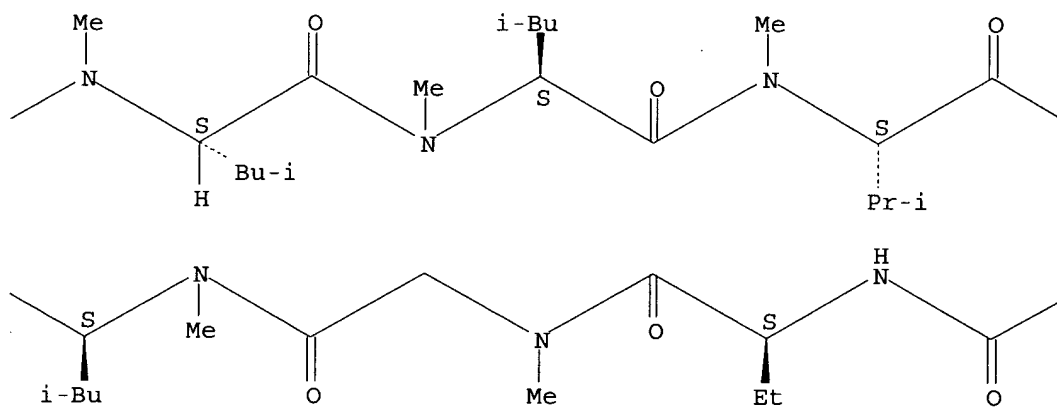
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-5-undecen-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

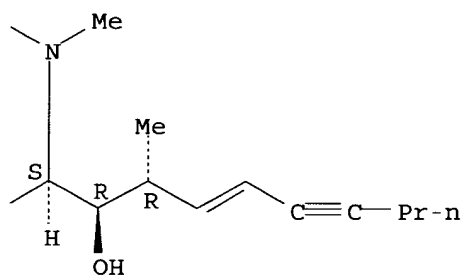
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PAGE 1-B



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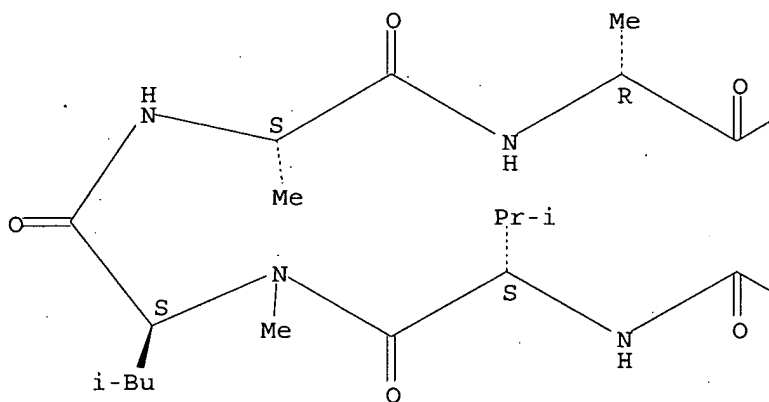


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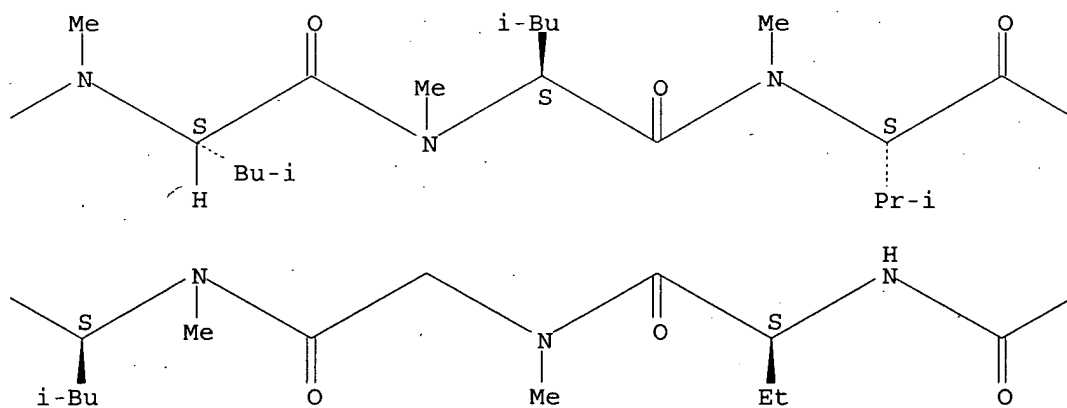
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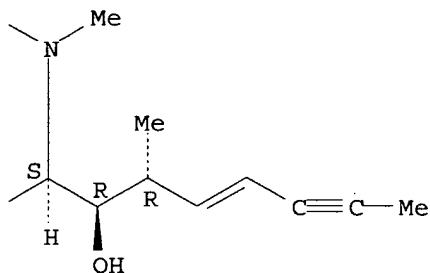
Absolute stereochemistry.
Double bond geometry unknown.

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IT 813426-88-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

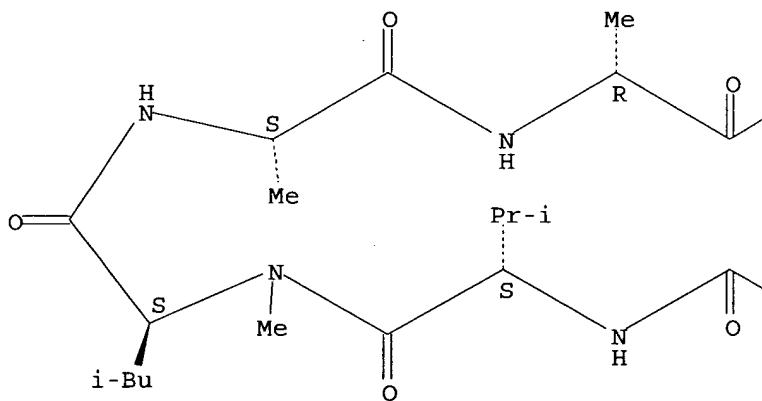
(preparation of cyclosporin derivs. for treatment of immune disorders)

RN 813426-88-9 HCAPLUS

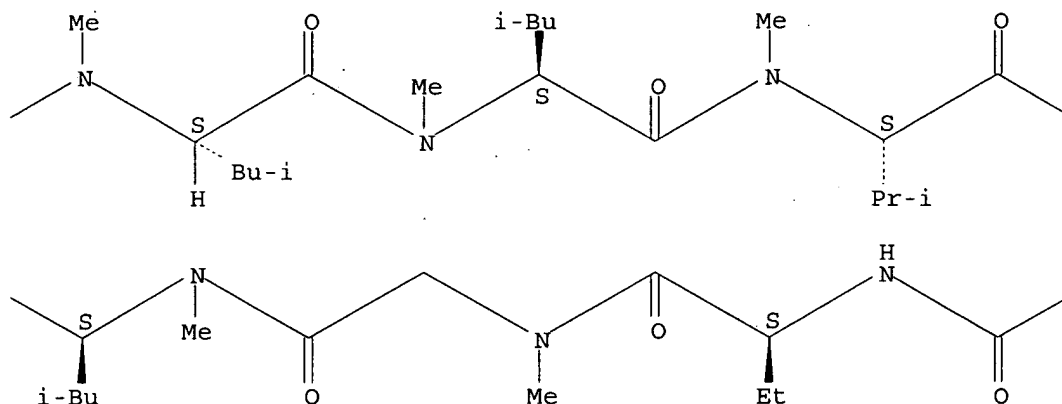
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-(acetyloxy)-4-methyl-2-(methylamino)-8-(trimethylsilyl)-5-octen-7-ynoic acid] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

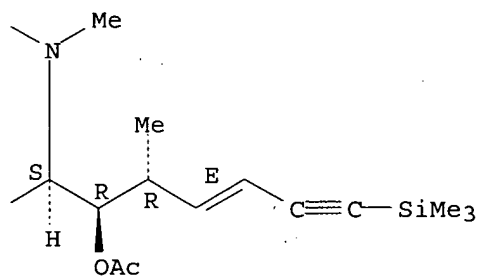
Double bond geometry as shown.



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L8 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:799453 HCAPLUS

DOCUMENT NUMBER: 141:296297

TITLE: Preparation of novel cyclosporins

INVENTOR(S): Molino, Bruce F.; Haydar, Simon N.; Yang, Zhicai; Michels, Peter C.; Hemenway, Michael S.; Rich, Joseph O.; Khmel'nitsky, Yuri

PATENT ASSIGNEE(S): Albany Molecular Research, Inc., USA

SOURCE: PCT Int. Appl., 249 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004082629	A2	20040930	WO 2004-US8118	20040316
WO 2004082629	A3	20051201		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
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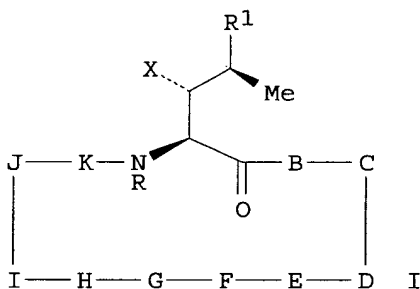
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 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.:

US 2003-455727P P 20030317
 WO 2004-US8118 W 20040316

OTHER SOURCE(S): MARPAT 141:296297
 GI



AB The invention relates cyclic peptides I [X is H, OH or a hydroxy group derivatized with an alkanoyl, aryloyl, alkyl-, aryl- or arylalkylaminocarbonyl or -oxycarbonyl group; R is H or Me; R1 is H, CHO, CH:CHCOMe, etc.; B, C, D, E, F, G, H, I, J, and K are certain amino acid residues] or their pharmaceutically-acceptable salts. Thus, cyclosporin A was converted to cyclosporin A Me vinyl ketone [R1 = (E)-2-butenyl to R1 = (E)-3-oxo-1-butenyl] by a biocatalytic method (HOBT-mediated laccase oxidation) or chemical methods using N-hydroxyphthalimide and benzoyl peroxide or tert-Bu hydroperoxide and sodium periodate.

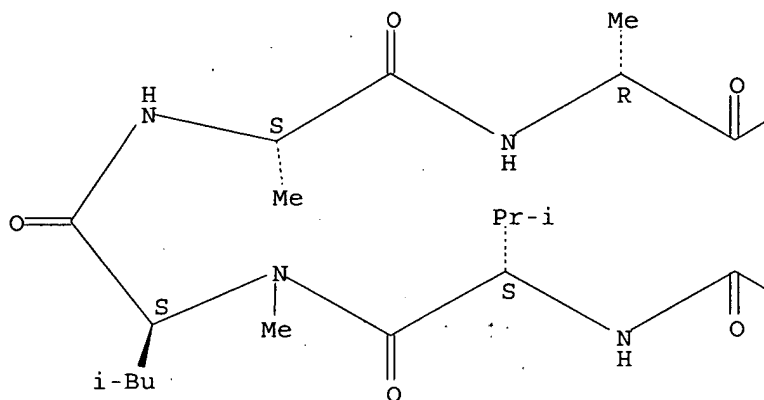
IT **761449-24-5P 761449-25-6P 761449-30-3P**
 RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (preparation of novel cyclosporins)

RN 761449-24-5 HCAPLUS

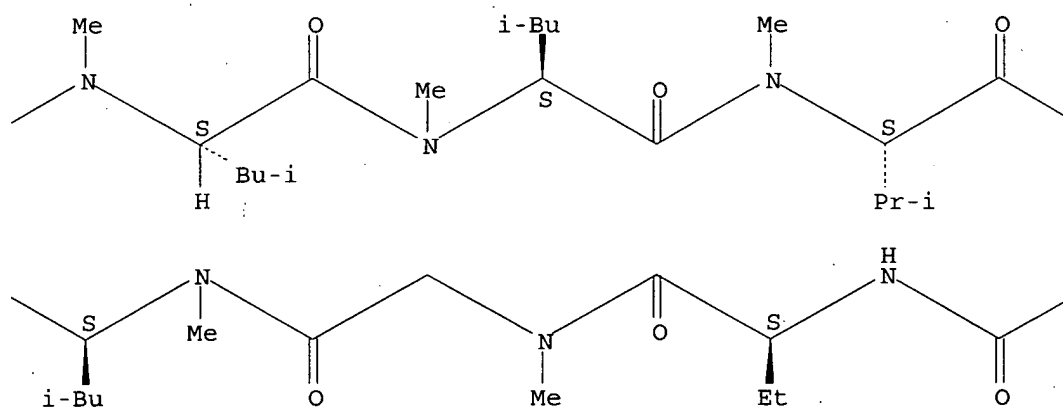
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-(acetyloxy)-4-methyl-2-(methylamino)-5,7-octadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

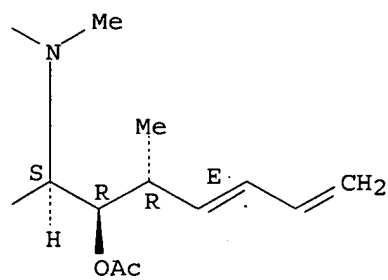
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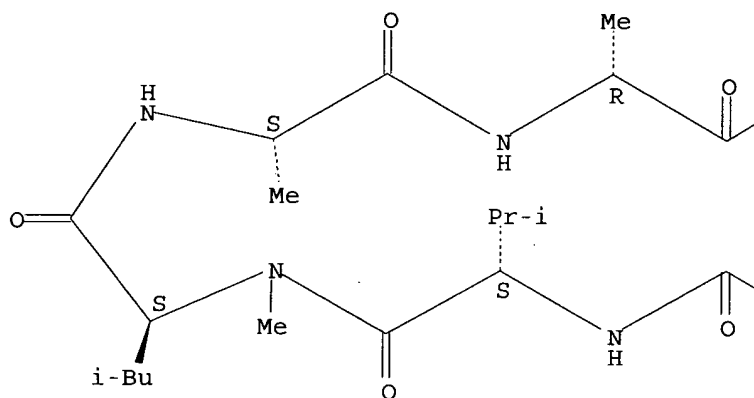


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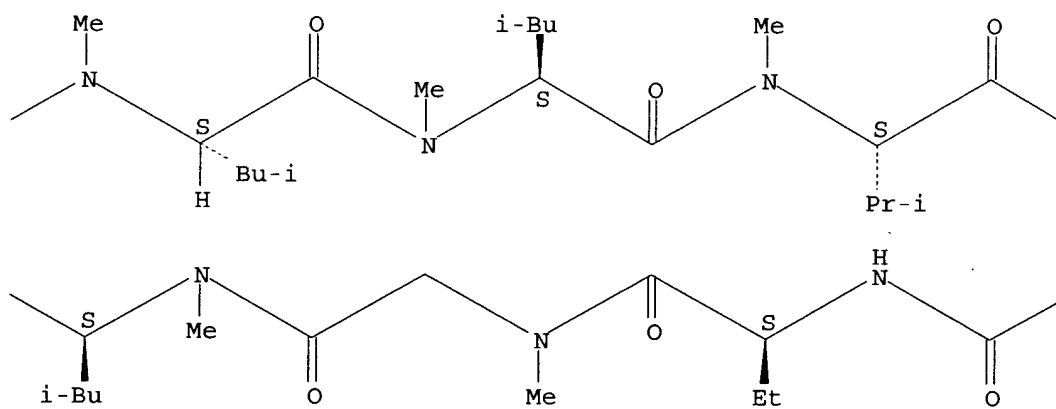
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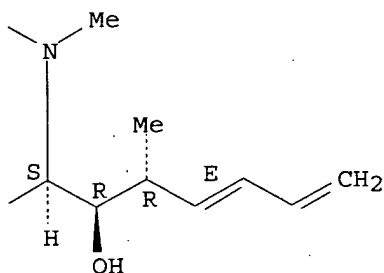
Absolute stereochemistry.
Double bond geometry as shown.

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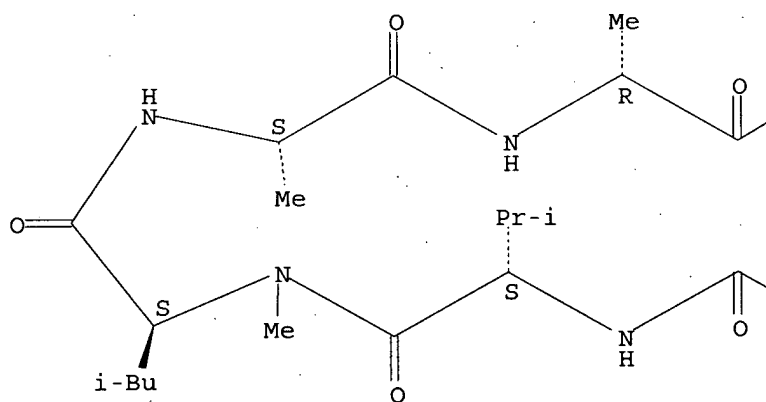




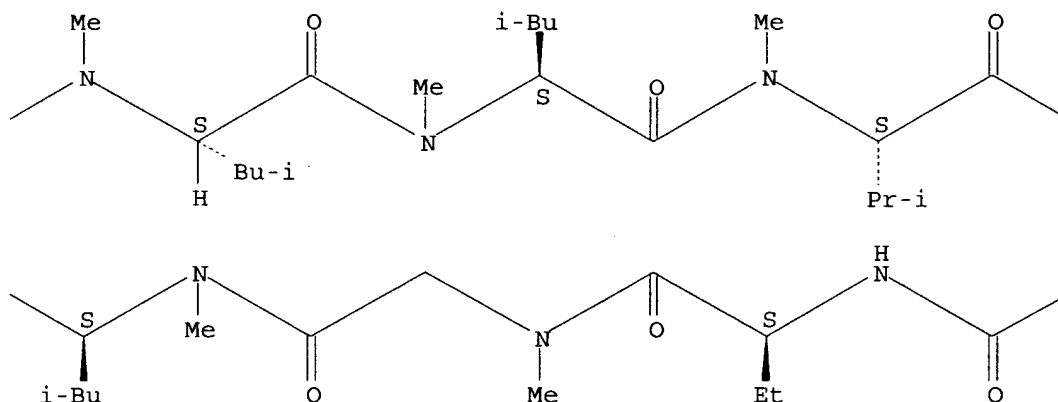
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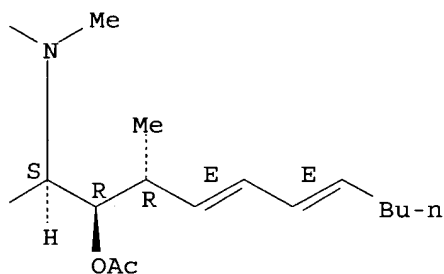
Absolute stereochemistry.
Double bond geometry as shown.



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IT 761448-95-7P 761448-96-8P 761448-97-9P

761449-26-7P 761449-27-8P, ALB 16085

761449-28-9P 761449-29-0P 761449-31-4P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);

PREP (Preparation); USES (Uses)

(preparation of novel cyclosporins)

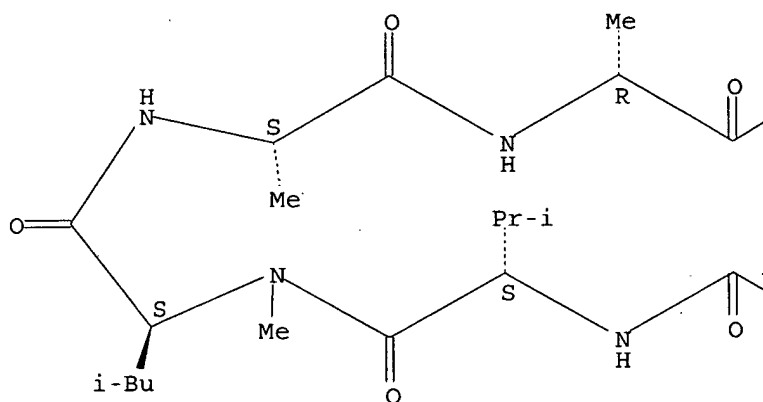
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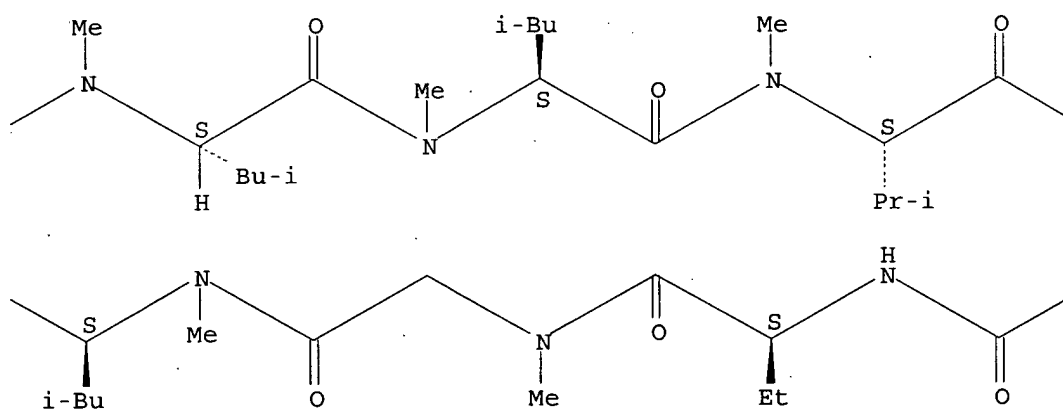
Absolute stereochemistry.

Double bond geometry as shown.

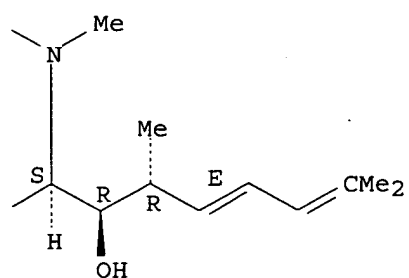
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PAGE 1-C

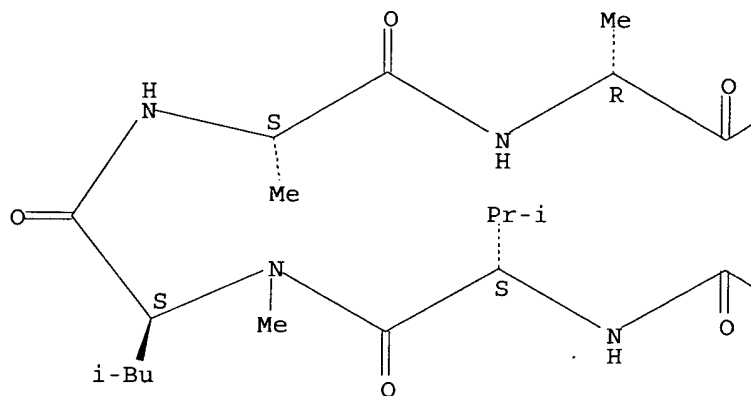


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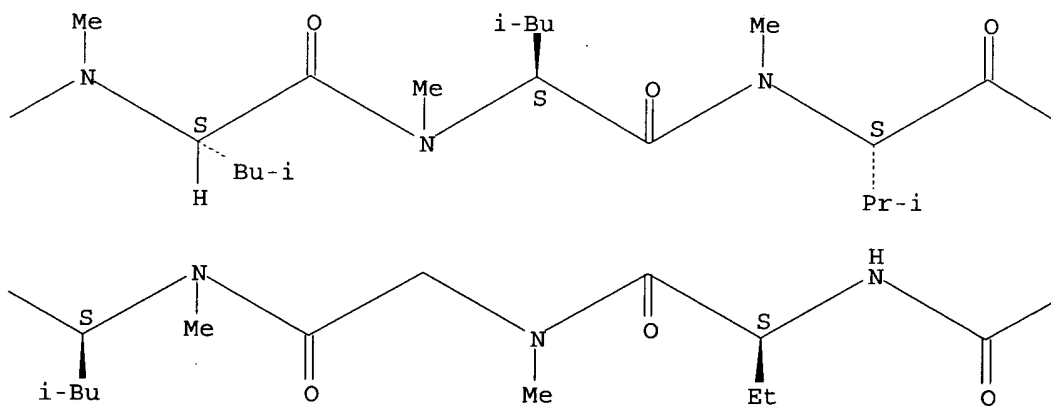
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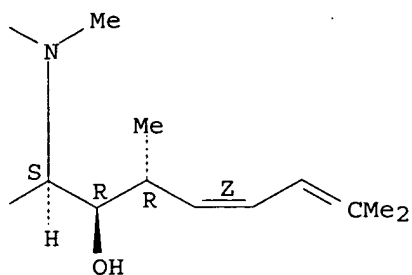
Absolute stereochemistry.
Double bond geometry as shown.

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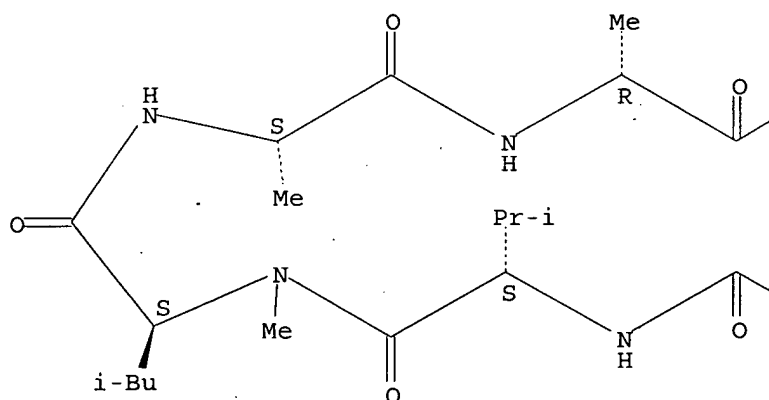




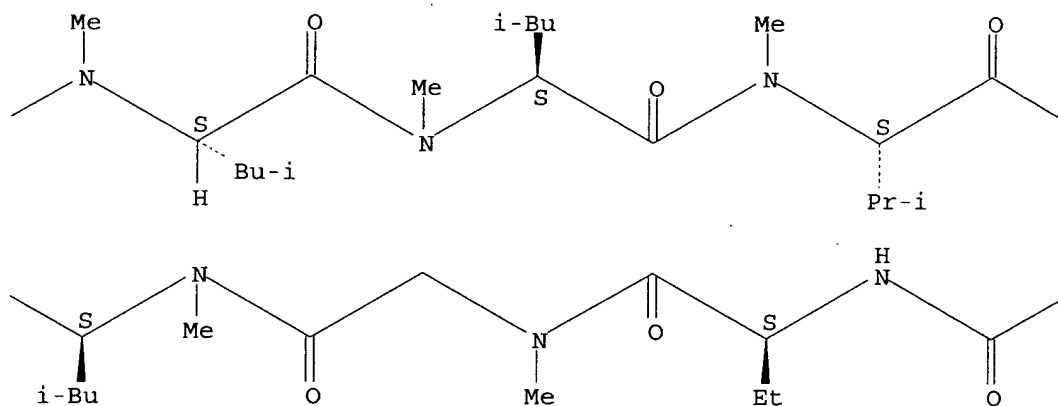
RN 761448-97-9 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-5,7-nonadienoic acid]- (9CI) (CA INDEX NAME)

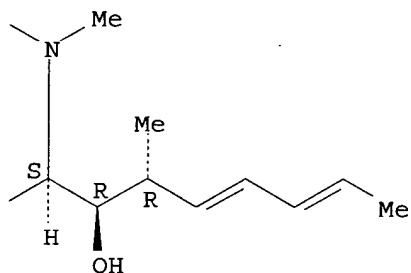
Absolute stereochemistry.
Double bond geometry unknown.



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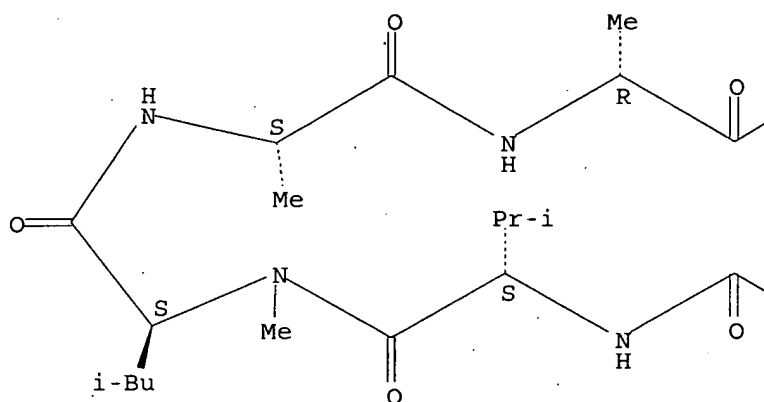


RN 761449-26-7 HCAPLUS

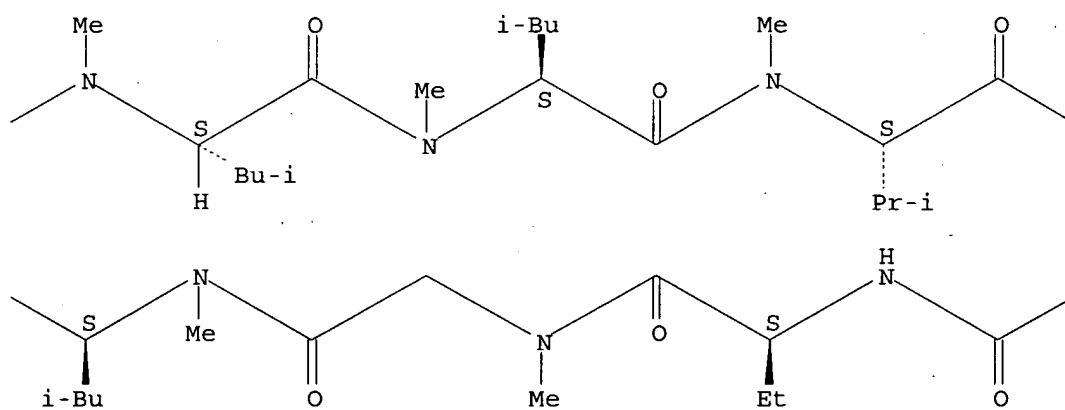
CN Cyclosporin A, 6-[(2S,3R,4R,5E,7E)-3-hydroxy-9-methoxy-4-methyl-2-(methylamino)-9-oxo-5,7-nonadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

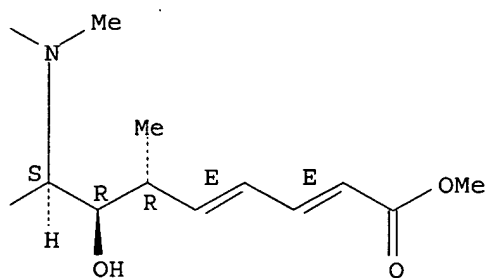
PAGE 1-A



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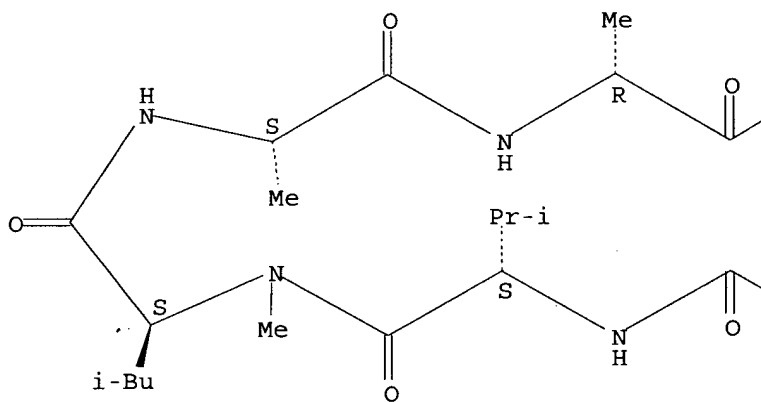


RN 761449-27-8 HCAPLUS

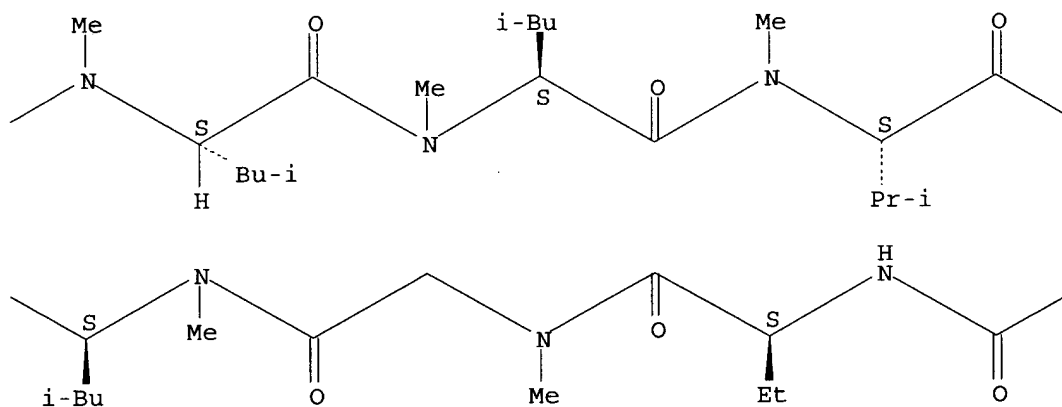
CN Cyclosporin A, 6-[(2S,3R,4R,5E,7E)-3-hydroxy-4-methyl-2-(methylamino)-8-phenyl-5,7-octadienoic acid]- (9CI) (CA INDEX NAME)

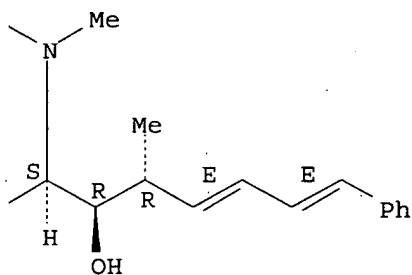
Absolute stereochemistry.
Double bond geometry as shown.

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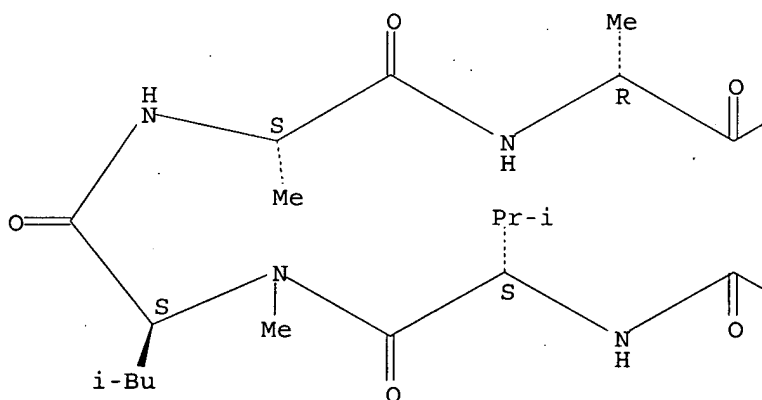




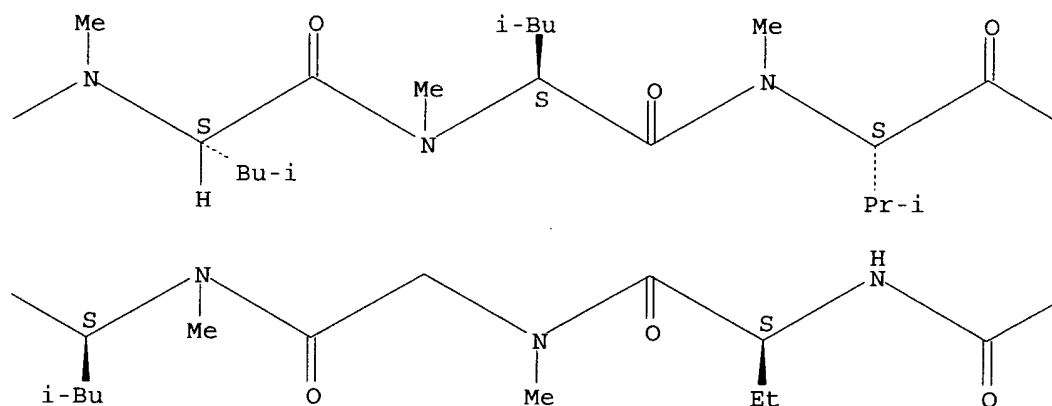
RN 761449-28-9 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,5E,7E)-8-cyclopentyl-3-hydroxy-4-methyl-2-(methylamino)-5,7-octadienoic acid]- (9CI) (CA INDEX NAME)

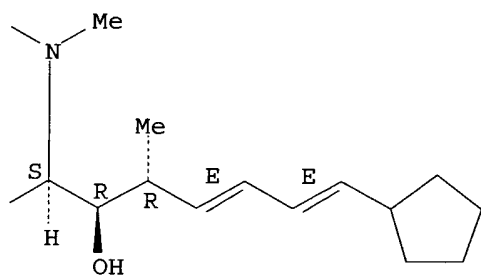
Absolute stereochemistry.
Double bond geometry as shown.



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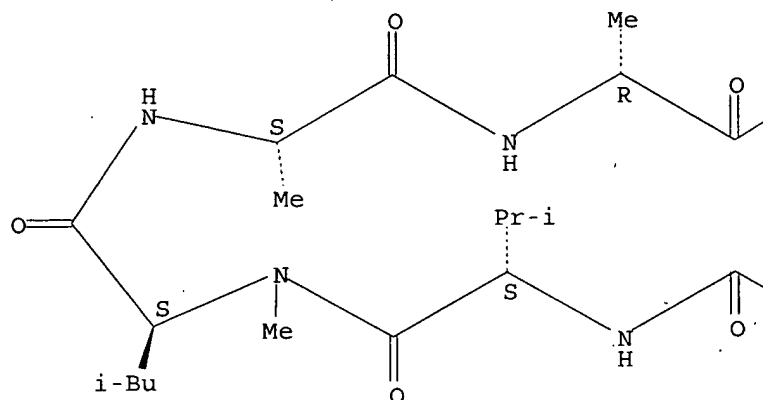


RN 761449-29-0 HCAPLUS

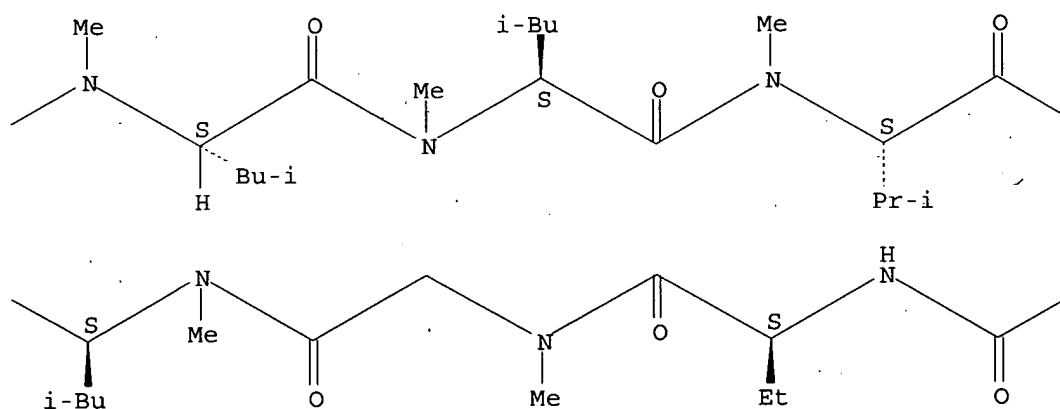
CN Cyclosporin A, 6-[(2S,3R,4R,5E,7E)-9,9,9-trifluoro-3-hydroxy-4-methyl-2-(methylamino)-5,7-nonadienoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

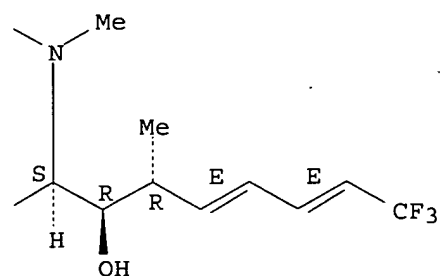
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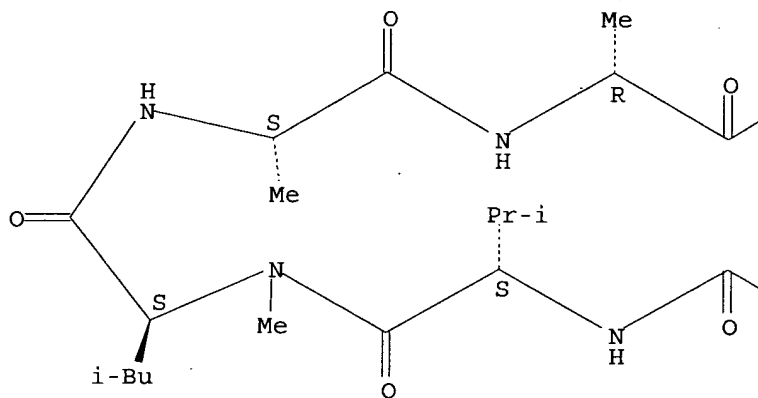


RN 761449-31-4 HCAPLUS

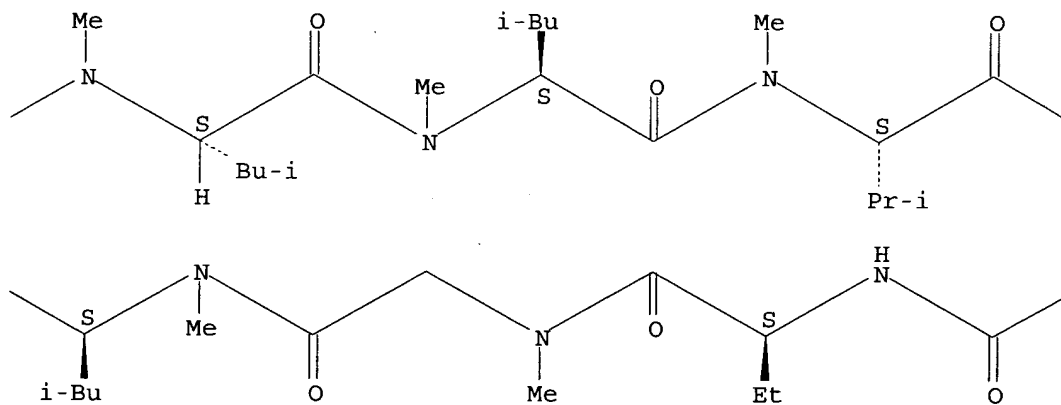
CN Cyclosporin A, 6-[(2S,3R,4R,5E,7E)-3-hydroxy-4-methyl-2-(methylamino)-5,7-dodecadienoic acid]- (9CI) (CA INDEX NAME)

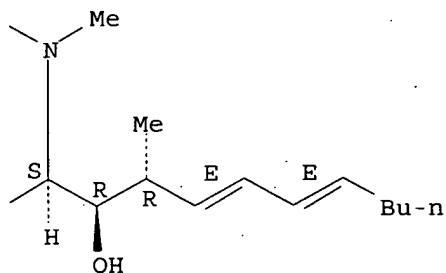
Absolute stereochemistry.
Double bond geometry as shown.

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IT 761449-64-3P 761449-68-7P 761449-70-1P

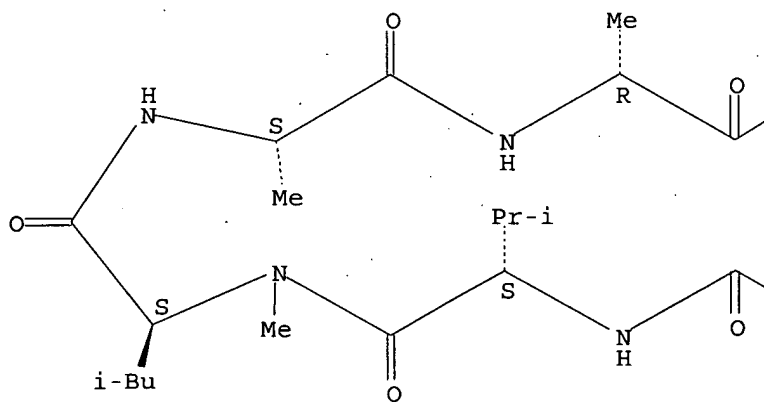
761449-71-2P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of novel cyclosporins)

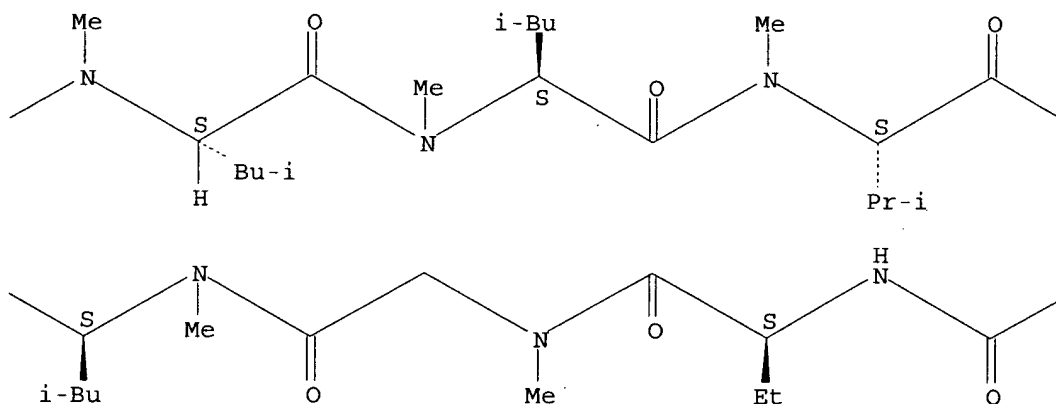
RN 761449-64-3 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-(acetyloxy)-4-methyl-2-(methylamino)-8-phenyl-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

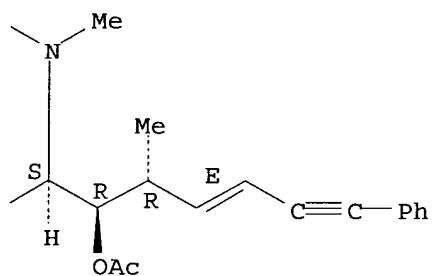
Absolute stereochemistry.
Double bond geometry as shown.



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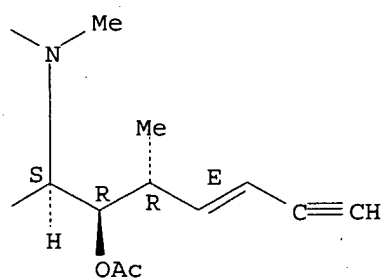
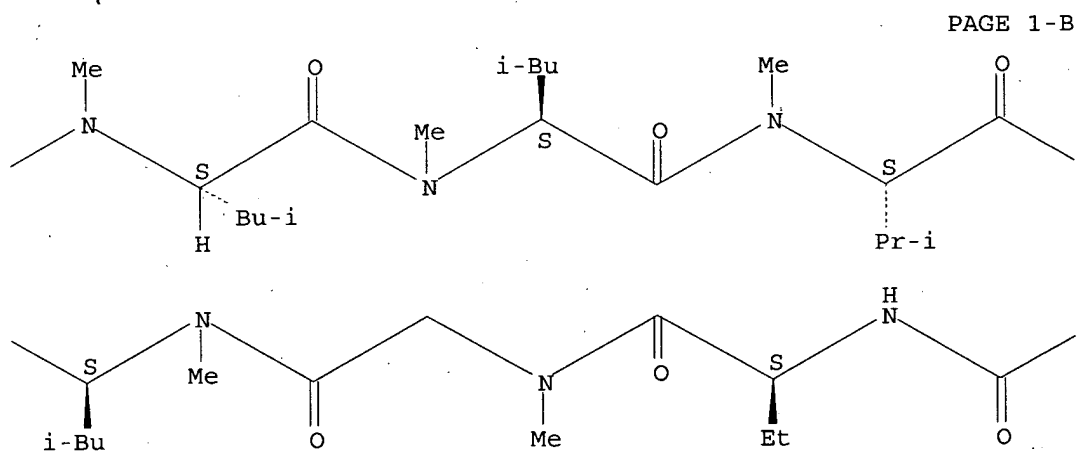
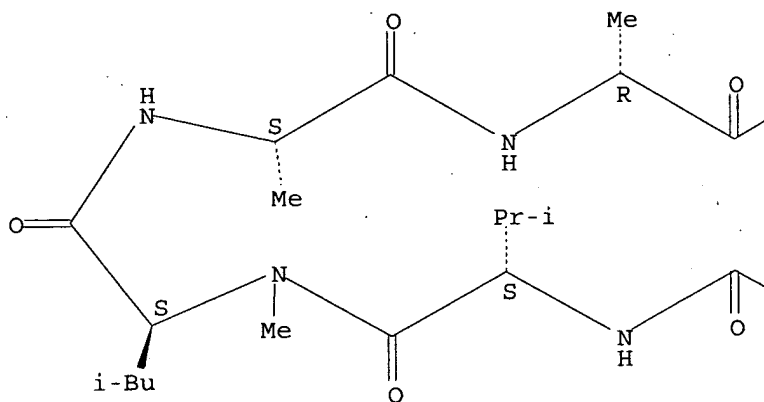
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RN 761449-68-7 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-(acetyloxy)-4-methyl-2-(methylamino)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

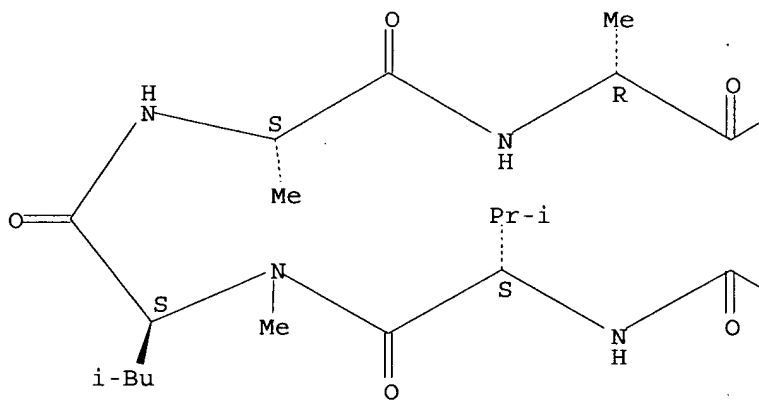


RN 761449-70-1 HCAPLUS

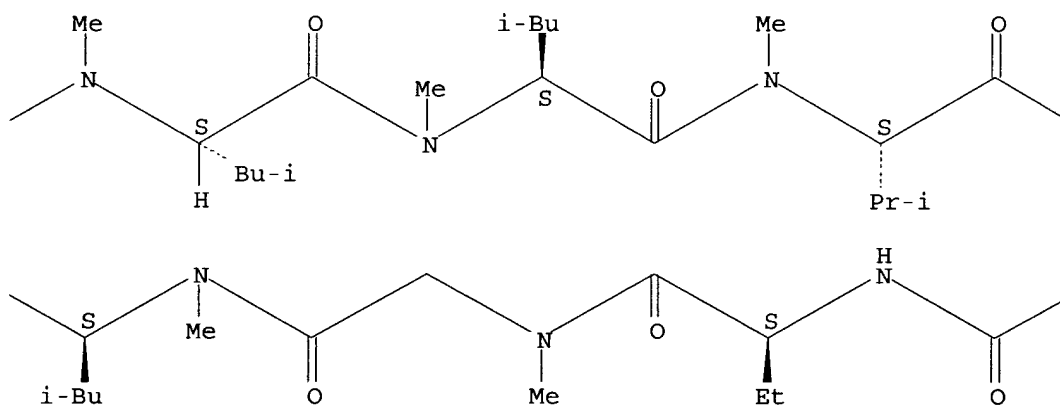
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-(acetyloxy)-4-methyl-2-(methylamino)-5-nonen-7-ynoic acid]- (9CI) (CA INDEX NAME)

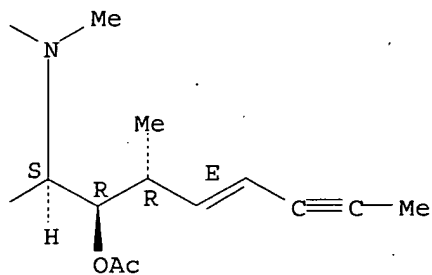
Absolute stereochemistry.
Double bond geometry as shown.

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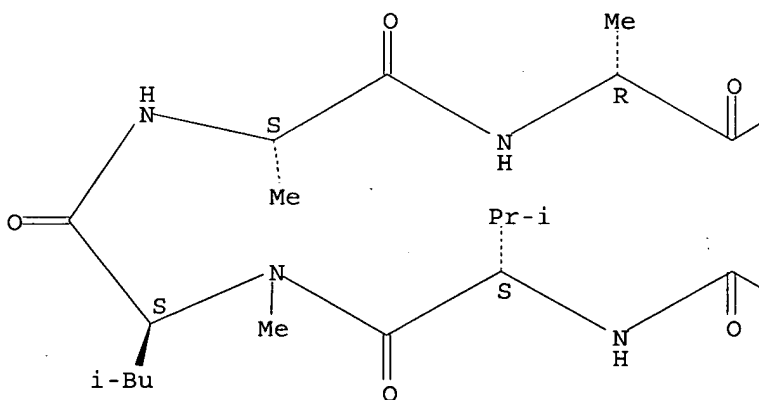




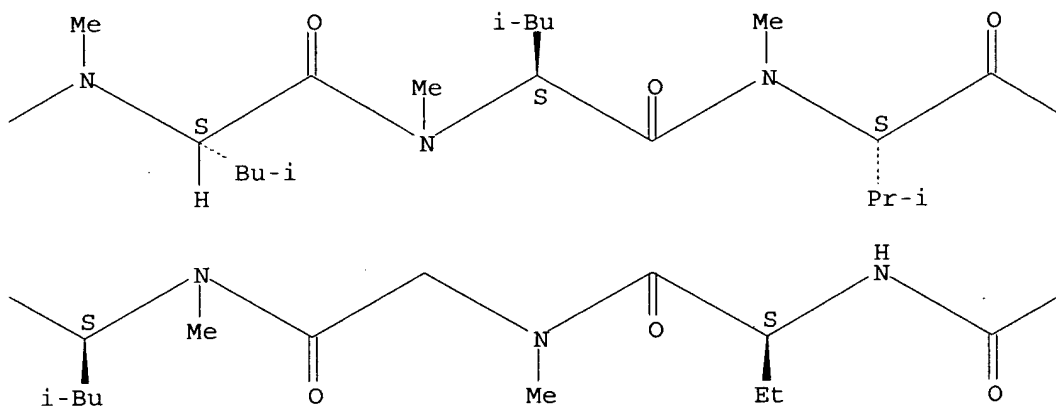
RN 761449-71-2 HCAPLUS

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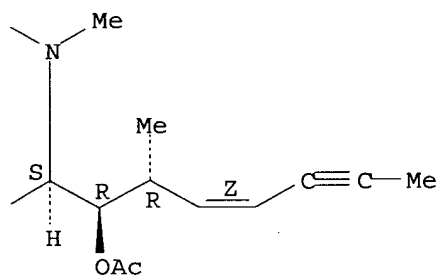
Absolute stereochemistry.
Double bond geometry as shown.



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IT 761449-65-4P 761449-66-5P 761449-67-6P
 761449-69-8P 761449-72-3P 761449-73-4P
 761449-74-5P 761450-04-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

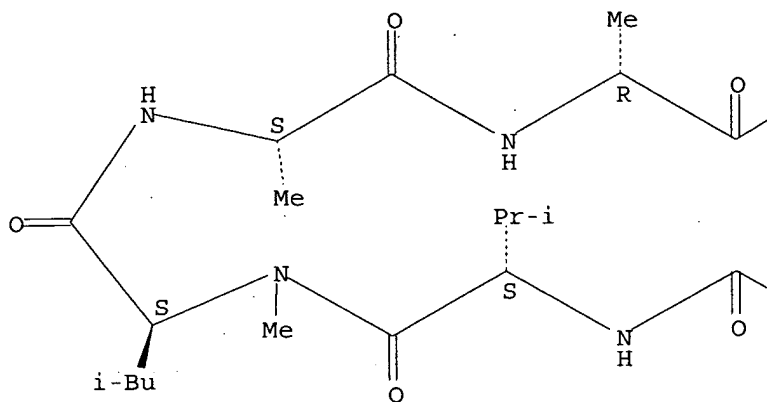
(preparation of novel cyclosporins)

RN 761449-65-4 HCAPLUS

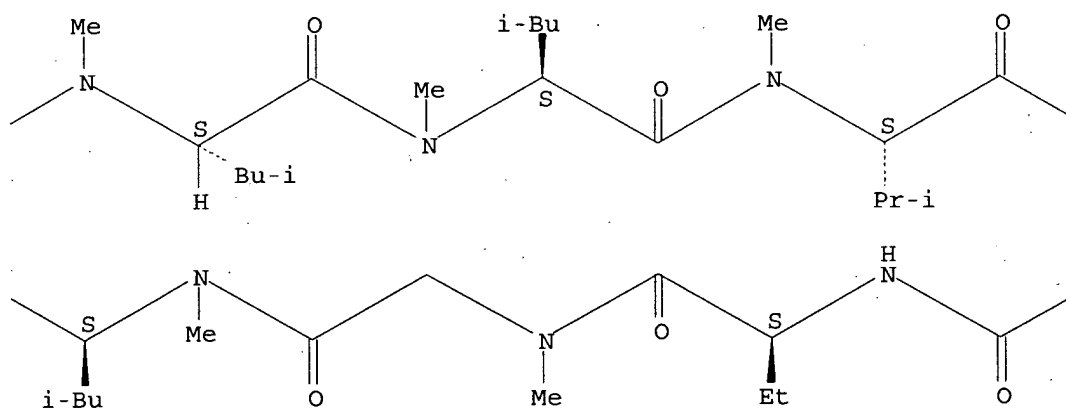
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-hydroxy-4-methyl-2-(methylamino)-8-phenyl-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

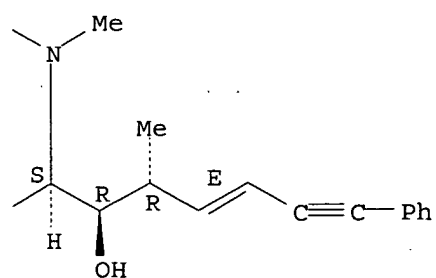
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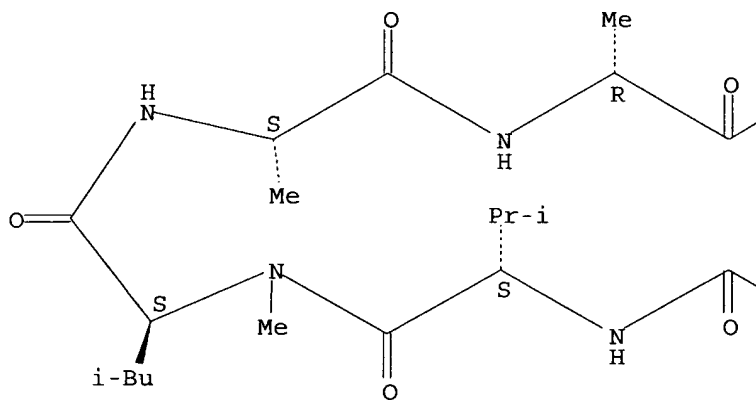


RN 761449-66-5 HCAPLUS

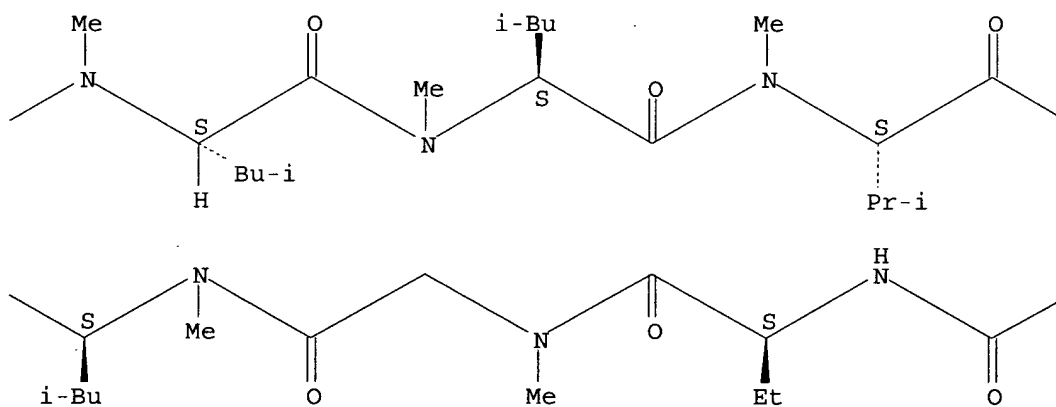
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-hydroxy-4-methyl-2-(methylamino)-8-(3-thienyl)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

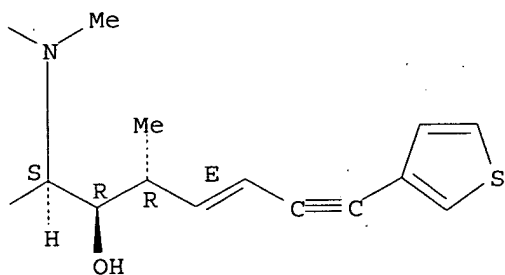
Absolute stereochemistry.
Double bond geometry as shown.

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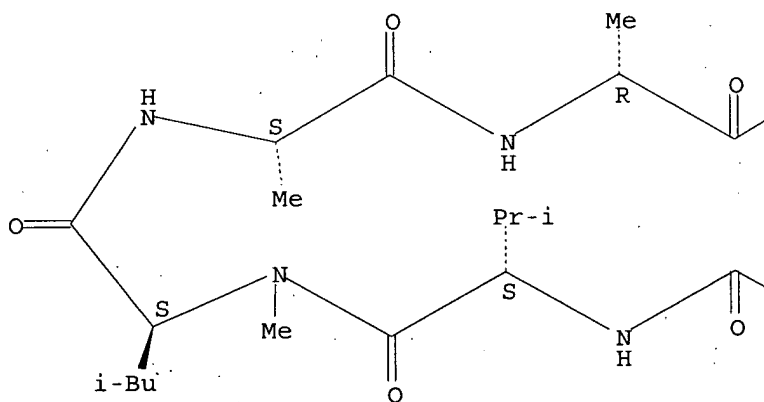




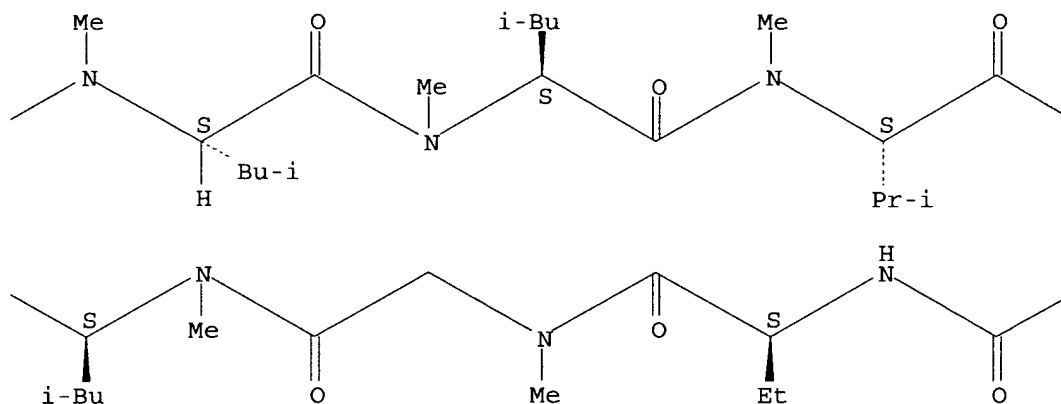
RN 761449-67-6 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,5Z)-3-hydroxy-4-methyl-2-(methylamino)-8-(3-thienyl)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

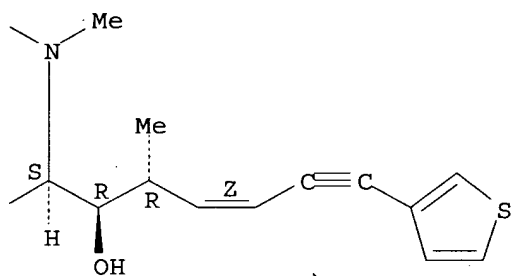
Absolute stereochemistry.
Double bond geometry as shown.



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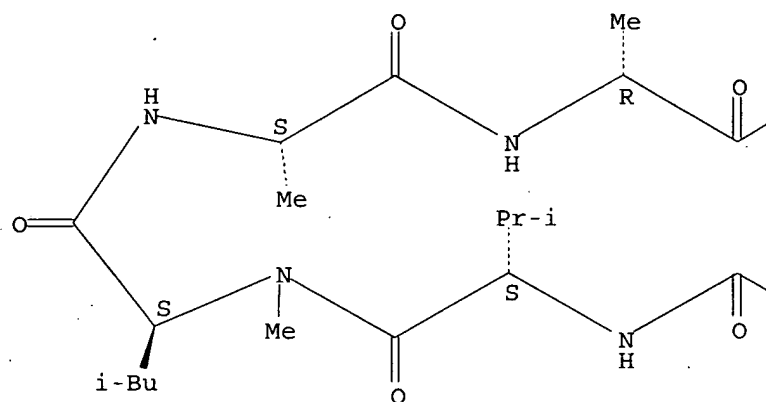


RN 761449-69-8 HCAPLUS

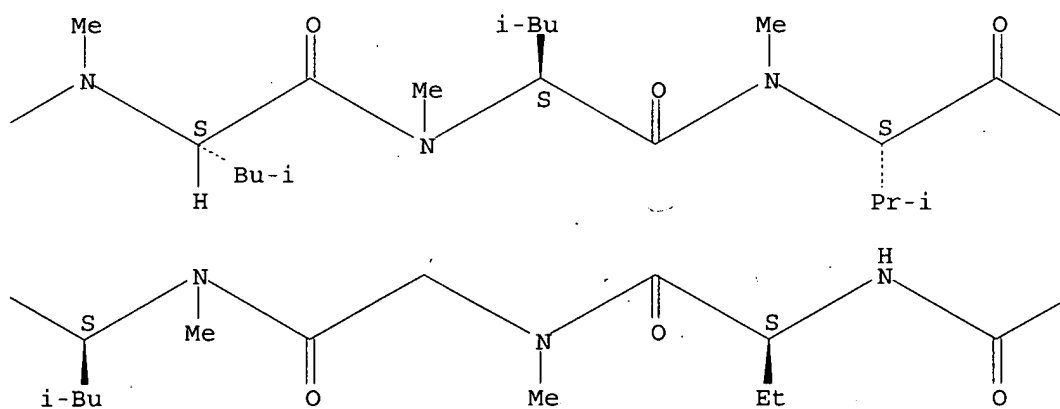
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-hydroxy-4-methyl-2-(methylamino)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

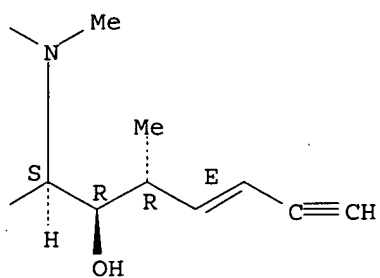
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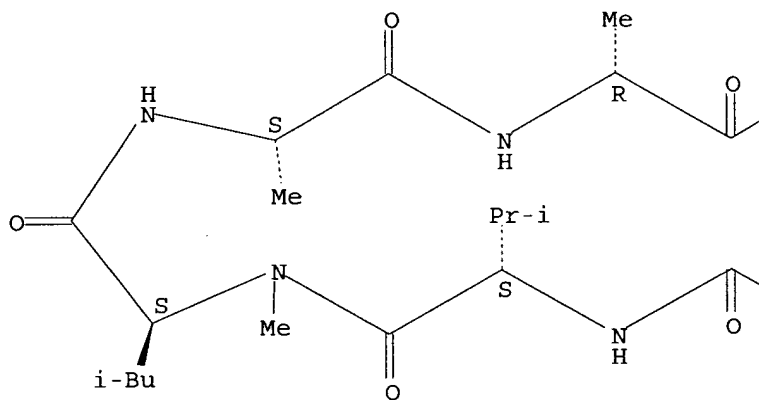


RN 761449-72-3 HCAPLUS

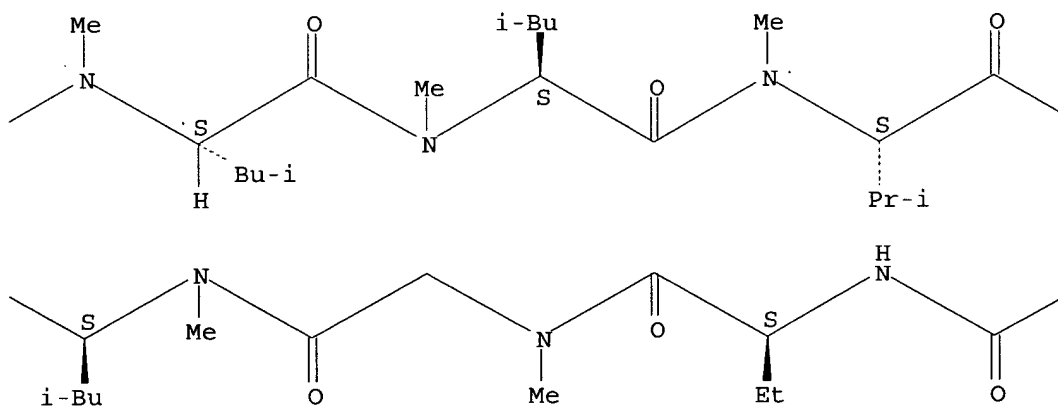
CN Cyclosporin A, 6-[(2S,3R,4R,5E)-3-hydroxy-4-methyl-2-(methylamino)-5-nonen-7-ynoic acid]- (9CI) (CA INDEX NAME)

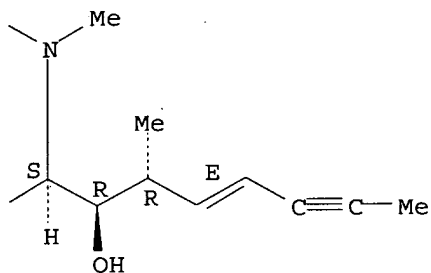
Absolute stereochemistry.
Double bond geometry as shown.

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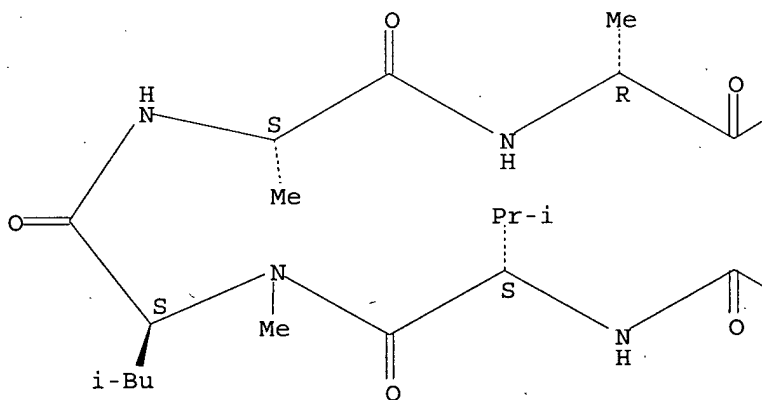




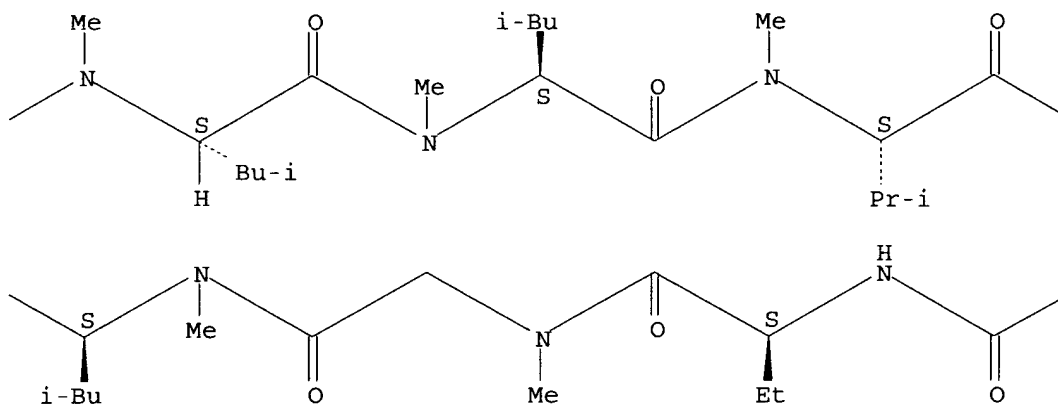
RN 761449-73-4 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,5Z)-3-hydroxy-4-methyl-2-(methylamino)-5-nonen-7-ynoic acid]- (9CI) (CA INDEX NAME)

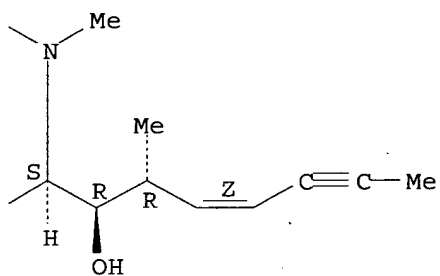
Absolute stereochemistry.
Double bond geometry as shown.



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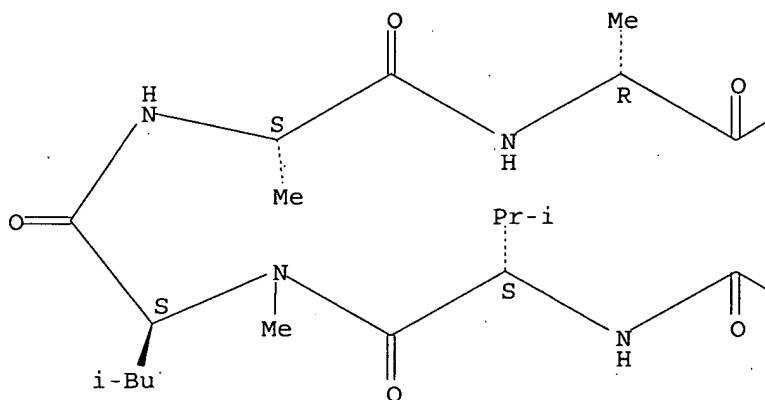


RN 761449-74-5 HCAPLUS

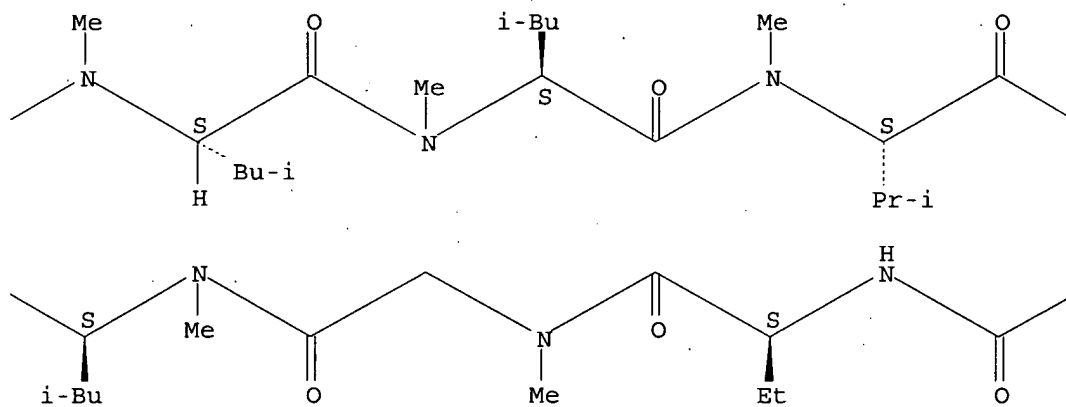
CN Cyclosporin A, 6-[(2S,3R,4R,5Z)-3-hydroxy-4,9-dimethyl-2-(methylamino)-5,9-decadien-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

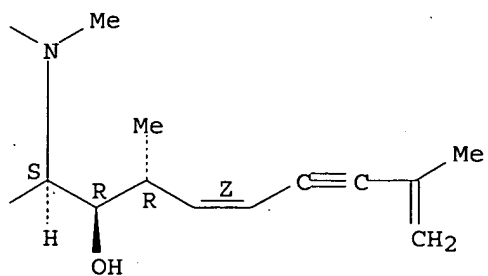
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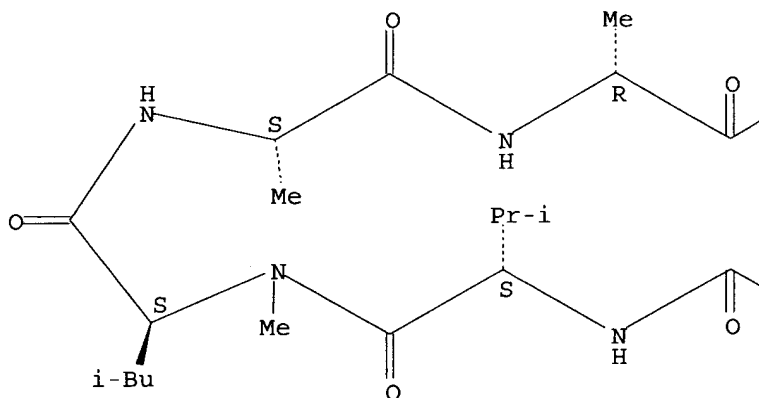


RN 761450-04-8 HCAPLUS

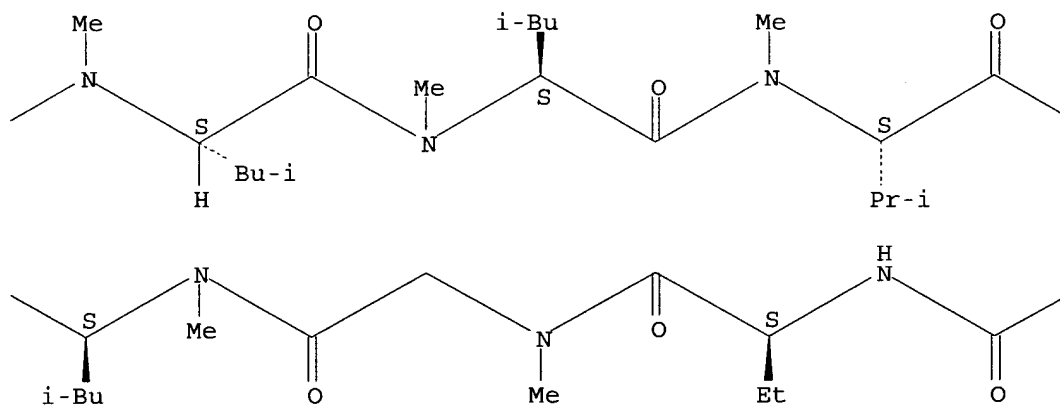
CN Cyclosporin A, 6-[(2S,3R,4R)-3-(acetyloxy)-4-methyl-2-(methylamino)-5,7-nonadienoic acid]- (9CI) (CA INDEX NAME)

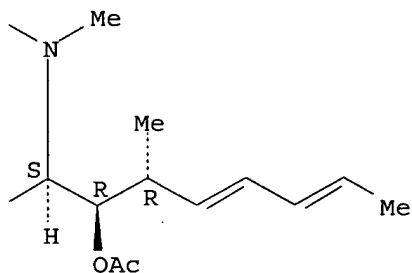
Absolute stereochemistry.
Double bond geometry unknown.

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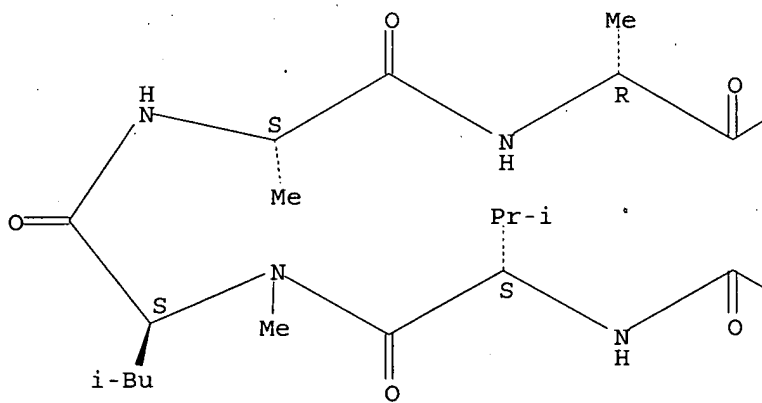
IT 761449-98-3P 761449-99-4P 761450-00-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of novel cyclosporins)

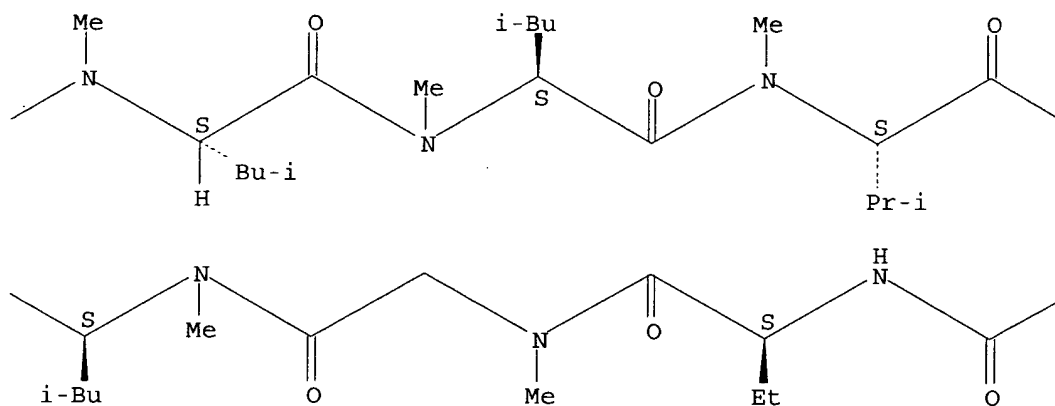
RN 761449-98-3 HCAPLUS

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(3-thienyl)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

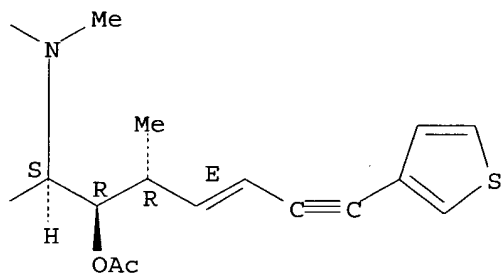
Absolute stereochemistry.
Double bond geometry as shown.



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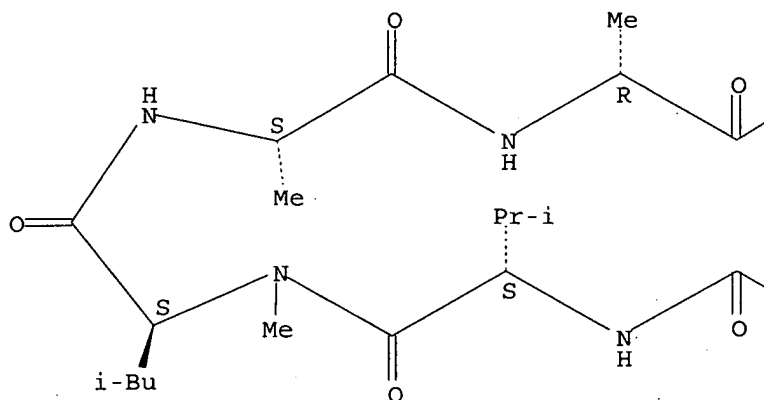


RN 761449-99-4 HCAPLUS

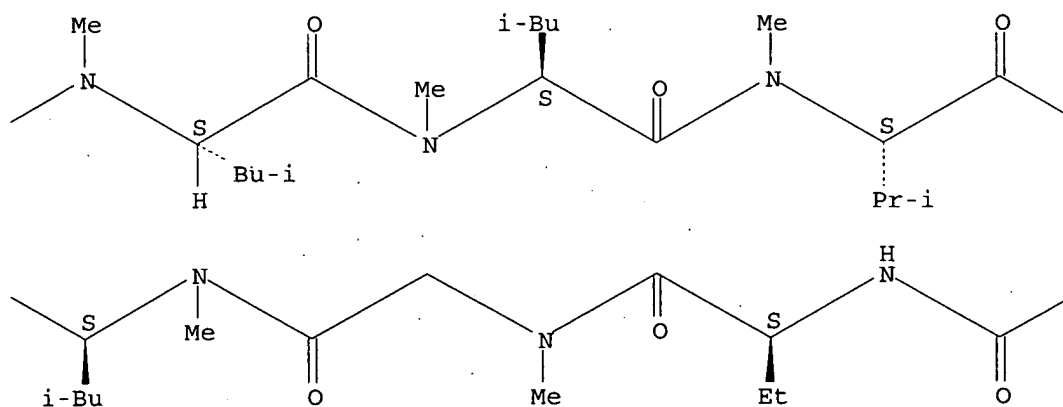
CN Cyclosporin A, 6-[(2S,3R,4R,5Z)-3-(acetyloxy)-4-methyl-2-(methylamino)-8-(3-thienyl)-5-octen-7-ynoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

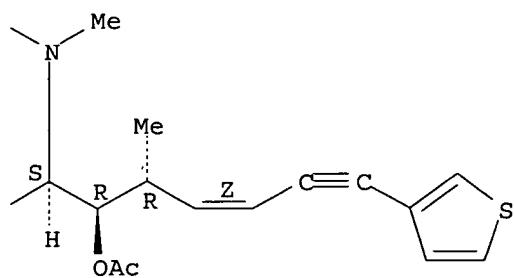
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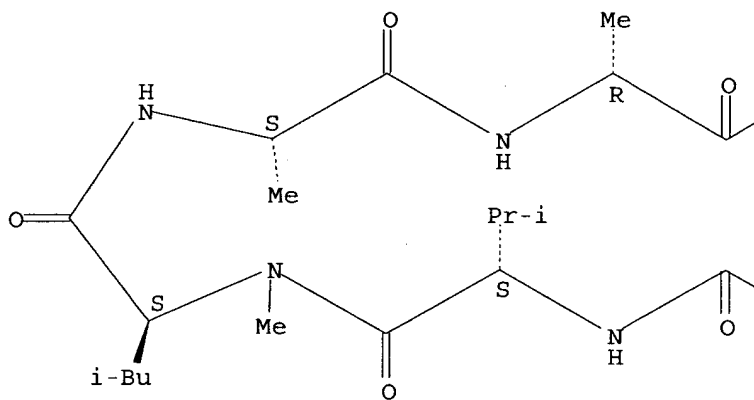


RN 761450-00-4 HCAPLUS

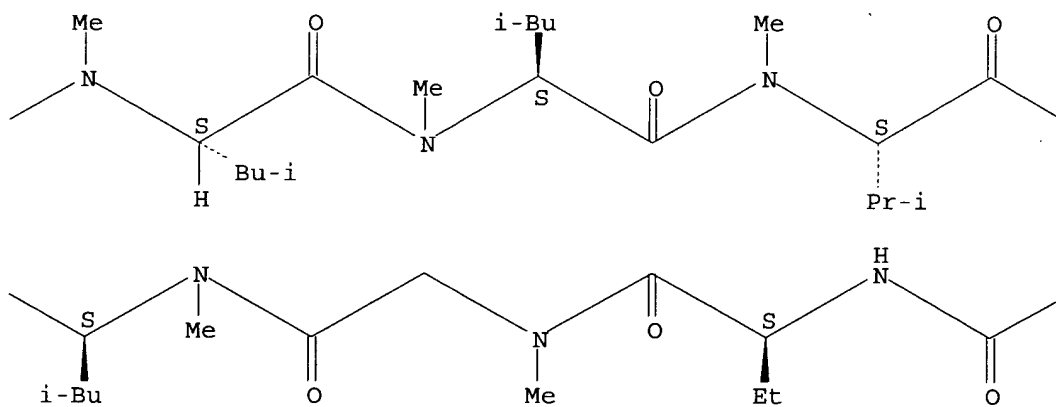
CN Cyclosporin A, 6-[(2S,3R,4R,5Z)-3-(acetyloxy)-4,9-dimethyl-2-(methylamino)-5,9-decadien-7-ynoic acid]- (9CI) (CA INDEX NAME)

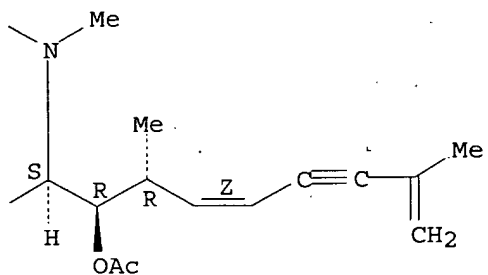
Absolute stereochemistry.
Double bond geometry as shown.

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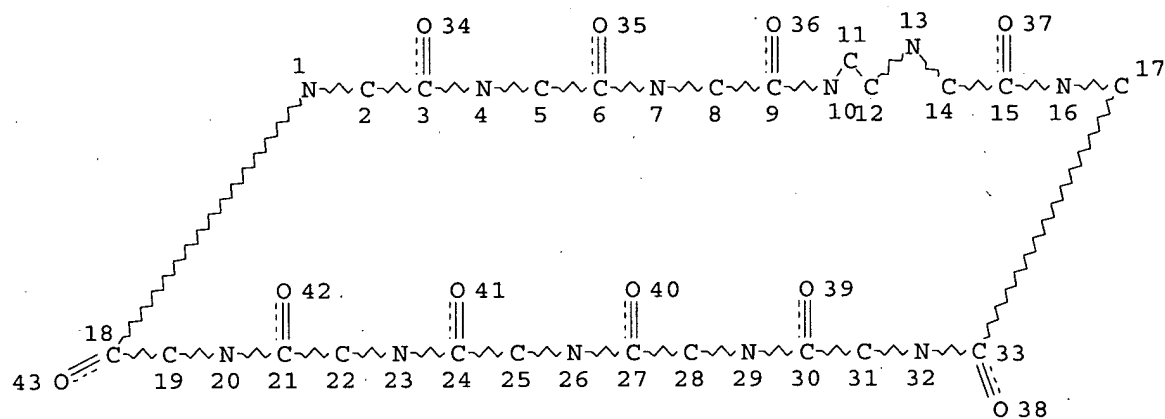


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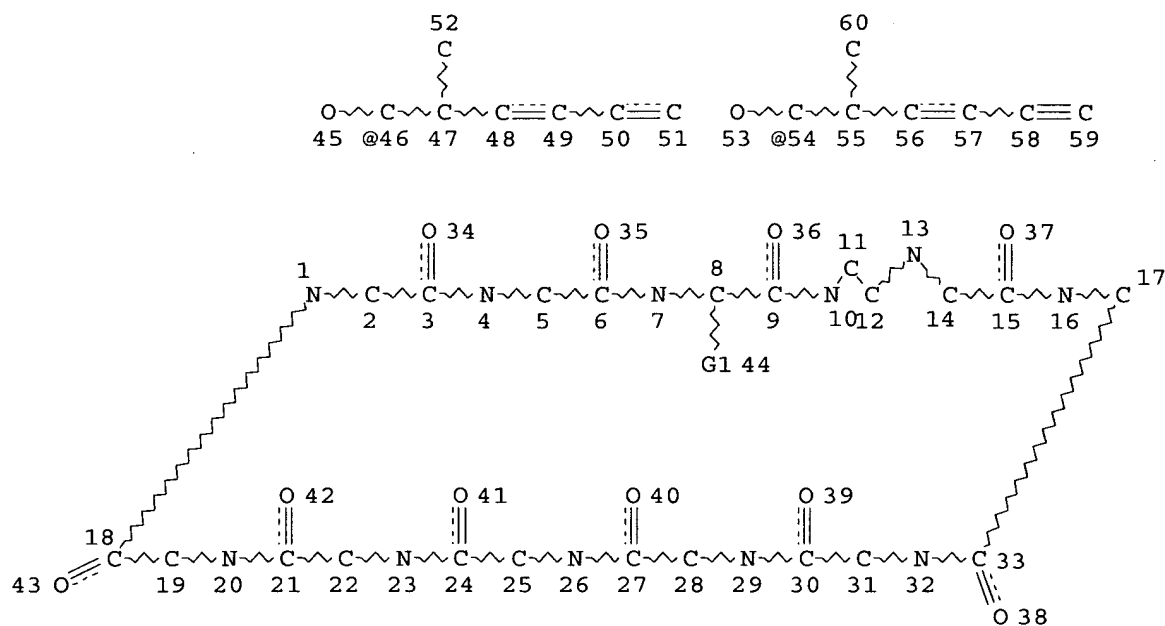
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L3 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 43

STEREO ATTRIBUTES: NONE
L5 1743 SEA FILE=REGISTRY SSS FUL L3
L6 STR



VAR G1=46/54

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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 60

STEREO ATTRIBUTES: NONE

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L8 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

L9 42 SEA FILE=HCAPLUS ABB=ON PLU=ON "WU FRANK"/AU OR "WU FRANK X
H"/AU

L12 41 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 NOT L8

=>

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L12 ANSWER 1 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:611823 HCAPLUS

DOCUMENT NUMBER: 143:153709

TITLE: Synthesis of macrocyclic hepatitis C virus (HCV)
serine protease NS3 inhibitors

INVENTOR(S): Miao, Zhenwei; Sun, Ying; Nakajima, Suanne; Tang,
Datong; **Wu, Frank**; Xu, Guoyou; Or, Yat S.;
Wang, Zhe

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 229 pp.

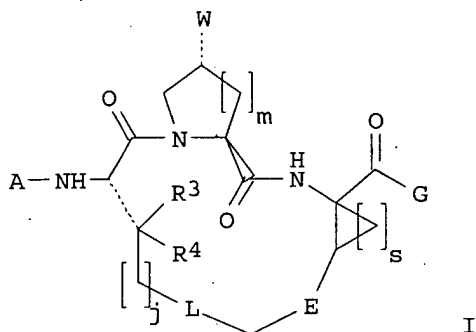
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005153877	A1	20050714	US 2004-774047	20040206
PRIORITY APPLN. INFO.:			US 2003-509069P	P 20030213
OTHER SOURCE(S):	MARPAT 143:153709			
GI				



AB The invention relates to cyclic peptides I [A = H, COR2, CO2R1, CONHR2, etc.; G = OH, alkoxy, NHSO2R1, CO2R1, CONHR1, etc.; L = absent, S, SO2, O, COCH2, CF2CH2, etc.; j = 0-4; m, s = 0-2; R1, R2 = H, C1-6-alkyl, (substituted)aryl, heteroaryl, etc.; R3, R4 = H, OH, Me, CN, SH, halo, NO2, NH2, amide, MeO, CF3O, CF3; E = CH:CH, CH2CH2; W = (un)substituted heterocyclic ring], or their pharmaceutically-acceptable salts, esters, or prodrugs, which inhibit serine protease activity, particularly the activity of HCV NS3-NS4A protease. An example is I (A = Me3CO2C, G = OH, L = absent, W = 5-phenyl-1,2,3,4-tetrazol-2-yl, j = 3, m, s = 1; R3, R4 = H), which was prepared via peptide coupling and ring-closing metathesis.

L12 ANSWER 2 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:372550 HCAPLUS

DOCUMENT NUMBER: 142:404795

TITLE: Recombinant human FIZZ3/resistin stimulates lipolysis in cultured human adipocytes, mouse adipose explants, and normal mice

AUTHOR(S): Ort, Tatiana; Arjona, Anibal A.; MacDougall, John R.; Nelson, Pam J.; Rothenberg, Mark E.; Wu, Frank; Eisen, Andrew; Halvorsen, Yuan-Di C.

CORPORATE SOURCE: CuraGen Corp., Branford, CT, 06405, USA
 SOURCE: Endocrinology (2005), 146(5), 2200-2209
 CODEN: ENDOAO; ISSN: 0013-7227

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human FIZZ3 (hFIZZ3) was identified as an ortholog of mouse resistin (mResistin), an adipocyte-specific secreted factor linked to insulin resistance in rodents. Unlike mResistin, hFIZZ3 is expressed in macrophages and monocytes, but is undetectable in adipose tissue. The profound macrophage infiltration of adipose that occurs during obesity suggests that hFIZZ3 may play an important role in adipocyte biol. Using

a recombinant protein produced in *Escherichia coli*, we report here that chronic treatment of cultured human adipocytes with hFIZZ3 results in hypotrophic cells with smaller lipid droplets. Recombinant hFIZZ3 facilitates preadipocyte proliferation and stimulates adipocyte triglyceride lipolysis, whereas recombinant mResistin inhibits adipocyte differentiation, with no detectable effect on proliferation or lipolysis. In addition, insulin-stimulated glucose uptake and Akt phosphorylation are not altered in hFIZZ3-treated adipocytes, indicating an intact insulin response. In mouse adipose explants, hFIZZ3 accelerates simultaneously triglyceride lipolysis and fatty acid reesterification, as assessed by measurement of glycerol and fatty acid release. Consistent with the in vitro findings, acute administration of recombinant hFIZZ3 into normal mice caused a significant increase in serum glycerol concentration with no elevation in free fatty acid at 45 min post injection. Taken together, the data suggest that recombinant hFIZZ3 can influence adipose metabolism by regulating preadipocyte cell number, adipocyte lipid content, and energy expenditure via accelerating the fatty acid/triglyceride futile cycle.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:99522 HCAPLUS

DOCUMENT NUMBER: 142:198355

TITLE: Preparation of aza-peptide macrocyclic hepatitis C serine protease inhibitors

INVENTOR(S): Wu, Frank X. H.; Nakajima, Suanne; Or, Yat

Sun; Lu, Zhi-hui; Sun, Ying; Miao, Zhenwei; Wang, Zhe

PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 75 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

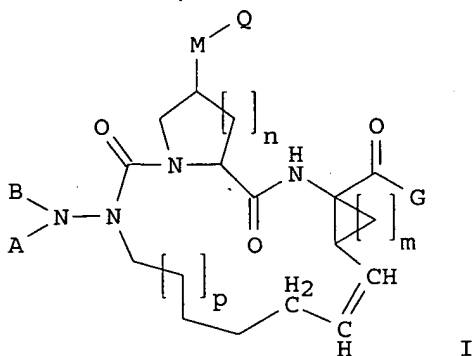
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005010029	A1	20050203	WO 2004-US15802	20040519
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

US 2005065073 A1 20050324 US 2003-613206 20030703

PRIORITY APPLN. INFO.: US 2003-613206 A 20030703

OTHER SOURCE(S): MARPAT 142:198355

GI



AB The invention relates to macrocyclic compds. I [A is H, CO₂H or an ester, acyl, (thio)carbamoyl or sulfonyl groups; B is H or alkyl; G is OH, alkoxy, amino, sulfonyl, acyl or carbamoyl groups; M is absent, O, S, NH or substituted imino; Q is (un)substituted aryl, heteroaryl or heterocycloalkyl; m, n = 0-2; p = 0-4] or their pharmaceutically-acceptable salts, esters or prodrugs which inhibit serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease. The compds. of the invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. Thus, compound I (A = Me₃CO₂C, B = H, G = OEt, M-Q = OEt, m = n = p = 1; stereo not shown) was prepared via N-acylation and cyclization reactions.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:698218 HCAPLUS

DOCUMENT NUMBER: 141:220883

TITLE: Macrocyclic hepatitis C virus (HCV) serine protease
 NS3 inhibitors, their synthesis and use to prevent HCV
 infection

INVENTOR(S): Miao, Zenwei; Sun, Ying; **Wu, Frank;**
Nakajima, Suanne; Xu, Guoyou; Or, Yat Sun; Wang, Zhe

PATENT ASSIGNEE(S) : Enanta Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 299 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

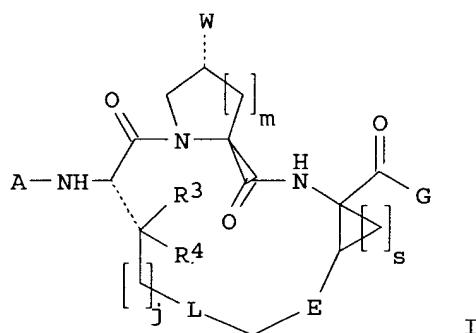
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072243	A2	20040826	WO 2004-US3479	20040206
WO 2004072243	A3	20051103		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004180815	A1	20040916	US 2003-384120	20030307

CA 2515216	AA	20040826	CA 2004-2515216	20040206
EP 1590442	A2	20051102	EP 2004-709020	20040206
EP 1590442	A3	20051221		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2003-360947 A 20030207
 US 2003-365854 A 20030213
 US 2003-384120 A 20030307
 WO 2004-US3479 W 20040206

OTHER SOURCE(S): MARPAT 141:220883
 GI



AB The present invention relates to compds. I [A = H, COR2, COOR1, CONHR2, etc.; G = OH, COR2, COOR1, CONHR1, etc.; L = S, SO2, O, COCH2, CF2CH2, etc.; j = 0-4; m, s = 0-2; R1,R2 = H, C1-6-alkyl, (substituted)aryl, heteroaryl, etc.; R3,R4 = H, OH, Me, CN, SH, halo, NO2, NH2, amide, MeO, CF3O, CF3; E = CH:CH, CH2CH2; W = (un)substituted heterocyclic ring], or a pharmaceutically acceptable salt, ester, or prodrug thereof, and to methods for their synthesis. The compds. inhibit serine protease activity, particularly the activity of HCV NS3-NS4A protease. Consequently, the compds. of the present invention interfere with the life cycle of HCV and are also useful as antiviral agents. The present invention further relates to pharmaceutical compns. comprising the aforementioned compds. for administration to a subject suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compds. of the present invention.

L12 ANSWER 5 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:757873 HCAPLUS

DOCUMENT NUMBER: 139:272083

TITLE: Protein and cDNA sequences of human secreted angioarrestin proteins involved in angiogenesis and therapeutic use thereof

INVENTOR(S): Dhanabal, Mohanraj; Wu, Frank; Larochelle, William J.; Lichenstein, Henri S.

PATENT ASSIGNEE(S): Curagen Corporation, USA

SOURCE: PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003078648	A2	20030925	WO 2003-US7586	20030311
WO 2003078648	A3	20041125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003224991	A1	20031204	US 2003-385802	20030311

PRIORITY APPLN. INFO.: US 2002-363266P P 20020311

AB The present invention is directed to novel mols., referred to herein as angioarrestin polypeptides, as well as nucleic acid sequences encoding those mols. Processes are also provided for producing a protein, which comprise growing a culture of host cells producing angioarrestin in a suitable culture medium, and purifying the protein from the culture. The present invention is also directed to Angioarrestin protein fragments, fusion proteins, and methods of use thereof. The invention includes a vector encoding the protein, the use of a therapeutic in the manufacture of a medicament for treating a angiogenic related syndromes associated with a human disease.

L12 ANSWER 6 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:519090 HCAPLUS

DOCUMENT NUMBER: 138:100457

TITLE: Angioarrestin: an antiangiogenic protein with tumor-inhibiting properties

AUTHOR(S): Dhanabal, Mohanraj; LaRochelle, William J.; Jeffers, Michael; Herrmann, John; Rastelli, Luca; McDonald, William F.; Chillakuru, Rajeev A.; Yang, Meijia; Boldog, Ferenc L.; Padigar, Muralidhara; McQueeney, Kelly D.; Wu, Frank; Minskoff, Stacey A.; Shimkets, Richard A.; Lichenstein, Henri S.

CORPORATE SOURCE: CuraGen Corp., Branford, CT, 06405, USA

SOURCE: Cancer Research (2002), 62(13), 3834-3841

CODEN: CNREAS; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The angiopoietins comprise a family of proteins that have pro or antiangiogenic activities. Through a proprietary technol. designed to identify transcripts of all expressed genes, we isolated a cDNA encoding an angiopoietin-related protein that we designate angioarrestin. The mRNA expression profile of angioarrestin was striking in that it was down-regulated in many tumor tissues when compared with adjacent nontumor tissue, suggesting a role for this protein in tumor inhibition. To test this hypothesis, we ectopically expressed angioarrestin in HT1080 tumor cells and measured pulmonary tumor nodule formation in nude mice. HT1080 cells expressing angioarrestin showed a marked reduction in the number and size of tumor nodules. In vitro, the recombinant protein was systematically tested in a number of endothelial cell assays and found to block critical processes involved in the angiogenic cascade, such as vascular endothelial growth factor/basic fibroblast growth factor-mediated endothelial cell proliferation, migration, tubular network formation, and adhesion to extracellular matrix proteins. These findings reveal a novel function for

angioarrestin as an angiogenesis inhibitor and indicate that the mol. may be a potential cancer therapeutic.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:335824 HCAPLUS

DOCUMENT NUMBER: 137:61202

TITLE: Platelet-derived growth factor D: Tumorigenicity in mice and dysregulated expression in human cancer

AUTHOR(S): LaRochelle, William J.; Jeffers, Michael; Corvalan, Jose R. F.; Jia, Xiao-Chi; Feng, Xiao; Vanegas, Sandra; Vickroy, Justin D.; Yang, Xiao-Dong; Chen, Francine; Gazit, Gadi; Mayotte, Jane; Macaluso, Jennifer; Rittman, Beth; Wu, Frank; Dhanabal, Mohan; Herrmann, John; Lichenstein, Henri S.

CORPORATE SOURCE: CuraGen Corp., Branford, CT, 06405, USA

SOURCE: Cancer Research (2002), 62(9), 2468-2473

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Platelet-derived growth factor (PDGF) has been directly implicated in developmental and physiol. processes, as well as in human cancer and other proliferative disorders. We have recently isolated and characterized a novel protease-activated member of the PDGF family, PDGF D. PDGF D has been shown to be proliferative for cells of mesenchymal origin, signaling through PDGF receptors. Comprehensive and systematic PDGF D transcript anal. revealed expression in many cell lines derived from ovarian, renal, and lung cancers, as well as from astrocytomas and medulloblastomas. β PDGF receptor profiling further suggested autocrine signaling in several brain tumor cell lines. PDGF D transforming ability and tumor formation in SCID mice was further demonstrated. Exploiting a sensitive PDGF D sandwich ELISA using fully human monoclonal antibodies, PDGF D was detected at elevated levels in the sera of ovarian, renal, lung, and brain cancer patients. Immunohistochem. anal. confirmed PDGF D localization to ovarian and lung tumor tissues. Together, these data demonstrate that PDGF D plays a role in certain human cancers.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:108424 HCAPLUS

DOCUMENT NUMBER: 137:42479

TITLE: CDP and AP-2 mediated repression mechanism of the replication-dependent hamster histone H3.2 promoter

AUTHOR(S): Wu, Frank; Lee, Amy S.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, USC/Norris Comprehensive Cancer Center, Keck School of Medicine of the University of Southern California, Los Angeles, CA, 90089-9176, USA

SOURCE: Journal of Cellular Biochemistry (2001), 84(4), 699-707

CODEN: JCEBD5; ISSN: 0730-2312

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The replication-dependent hamster histone H3.2 promoter contains two tandem CCAAT repeats located upstream of the TATA element. It has been shown that the NF-Y/CBF complex binds to a single CCAAT motif with high

affinity, whereas the CCAAT displacement protein (CDP) binds to at least two CCAAT motifs in close proximity. Here, we report that the two CCAAT motifs within the H3.2 promoter confer transcriptional repression of the promoter during the cell cycle. While we cannot detect direct association of CDP with Rb in vitro, we discover that CDP can bind AP-2, a ubiquitous factor that interacts with Rb. The interaction domains between CDP and AP-2 are mapped to the highly conserved cut repeats of CDP as well as the basic and dimerization region of AP-2. Further, in transfection assays, CDP and AP-2 act synergistically to suppress the H3.2 promoter. Together, these data support a repression mechanism mediated by CDP and AP-2 that regulates H3.2 gene expression during the mammalian cell cycle.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:60983 HCAPLUS

DOCUMENT NUMBER: 135:118331

TITLE: YY1 as a regulator of replication-dependent hamster histone H3.2 promoter and an interactive partner of AP-2

AUTHOR(S): Wu, Frank; Lee, Amy S.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology and the University of Southern California/Norris Comprehensive Cancer Center, Keck School of Medicine of the University of Southern California, Los Angeles, CA, 90089-9176, USA

SOURCE: Journal of Biological Chemistry (2001), 276(1), 28-34
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In analyzing cis-regulatory elements important for cell cycle control of the replication-dependent hamster histone H3.2 gene, we discovered a binding site for the transcription factor YY1 embedded within GC-rich sequences between the two tandem CCAAT repeats proximal to the TATA element. Base mutations that specifically eliminated YY1 binding resulted in suppression of the S phase induction of the H3.2 promoter. In addition, we discovered that YY1 is an interactive partner of AP-2, which also binds the H3.2 promoter and regulates its cell cycle-dependent expression. The critical domains for YY1 and AP-2A interaction are mapped, revealing that the N-terminal portion of YY1 (amino acids 1-300) and the DNA-binding/dimerization region of AP-2A are required. Our results suggest that YY1, acting as a transcription factor binding to its site on the promoter, or through protein-protein interaction with AP-2, may be part of a regulatory network including key cell cycle regulators such as c-Myc and Rb in controlling growth-and differentiation-regulated gene expression.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:412697 HCAPLUS

DOCUMENT NUMBER: 133:130996

TITLE: Activation of the cytoplasmic c-Abl tyrosine kinase by reactive oxygen species

AUTHOR(S): Sun, Xiangao; Majumder, Pradip; Shioya, Hasashi;

Wu, Frank; Kumar, Shailendra; Weichselbaum, Ralph; Kharbanda, Surender; Kufe, Donald

CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Journal of Biological Chemistry (2000), 275(23),
17237-17240
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular
Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ubiquitously expressed c-Abl protein tyrosine kinase localizes to both
the nucleus and cytoplasm. The nuclear form of c-Abl is activated in the
cellular response to genotoxic stress. Cytoplasmic c-Abl is activated by
oxidative stress. The mitochondrial cytochrome c is released in the
cellular response to H₂O₂ and this effect is mediated by a c-Abl-dependent
mechanism. Thus, H₂O₂-induced apoptosis is attenuated in c-Abl-deficient
cells. Apparently, cytoplasmic c-Abl is involved in the apoptotic
response of cells to oxidative stress.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:208587 HCAPLUS
DOCUMENT NUMBER: 132:332578
TITLE: Interaction between protein kinase C δ and the
c-Abl tyrosine kinase in the cellular response to
oxidative stress
AUTHOR(S): Sun, Xiangao; **Wu, Frank**; Datta, Rakesh;
Kharbanda, Surender; Kufe, Donald
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School,
Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (2000), 275(11),
7470-7473
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular
Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase C (PKC) isoforms are phosphorylated on tyrosine in the
response of cells to oxidative stress. The present studies demonstrate
that treatment of cells with hydrogen peroxide (H₂O₂) induces binding of
the PKC δ isoform and the c-Abl protein-tyrosine kinase. The results
show that c-Abl phosphorylates PKC δ in the H₂O₂ response. We also
show that PKC δ phosphorylates and activates c-Abl in vitro. In
cells, induction of c-Abl activity by H₂O₂ is attenuated by the PKC δ
inhibitor, rottlerin, and by overexpression of the regulatory domain of
PKC δ . These findings support a functional interaction between
PKC δ and c-Abl in the cellular response to oxidative stress.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:16944 HCAPLUS
DOCUMENT NUMBER: 130:193461
TITLE: Analysis of neuronal nitric oxide synthase isoform
expression and identification of human nNOS- μ
AUTHOR(S): Lin, Ching-Shwun; Lau, Angie; Bakircioglu, Emre; Tu,
Richard; **Wu, Frank**; Week, Susan; Nunes,
Lora; Lue, Tom F.
CORPORATE SOURCE: Knuppe Molecular Urology Laboratory, Department of
Urology, University of California, San Francisco, San
Francisco, CA, 94143, USA
SOURCE: Biochemical and Biophysical Research Communications

(1998), 253(2), 388-394
CODEN: BBRC9; ISSN: 0006-291X

PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuronal form of nitric oxide synthase (nNOS) is responsible for the production of NO, which acts as a neurotransmitter for penile erection and urethra relaxation. An nNOS splice variant form, nNOS- μ , was first reported to be specifically expressed in skeletal muscle and heart in the rat, but later also identified in rat penile cavernosum. The authors report an apparently universal expression of nNOS- μ mRNA in rat tissues, including brain, which was previously reported to be lacking nNOS- μ . Immunoblot anal. revealed that some com. available nNOS antibodies had high levels of nonspecific activities, which could lead to the appearance of seemingly multiple forms of nNOS. Immunohistochem. anal. with these antibodies also produced nonspecific stainings. In humans, nNOS- μ expression appeared to be confined to skeletal muscle and heart. Human penile tissues obtained from patients with erectile dysfunction did not express nNOS- μ . The human nNOS- μ -specific cDNA sequence was 89% homologous to its rat counterpart. (c) 1998 Academic Press.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:746357 HCAPLUS

DOCUMENT NUMBER: 130:120351

TITLE: Identification of AP-2 as an interactive target of Rb and a regulator of the G1/S control element of the hamster histone H3.2 promoter

AUTHOR(S): Wu, Frank; Lee, Amy S.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology and the USC/Norris Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles, CA, 90033, USA

SOURCE: Nucleic Acids Research (1998), 26(21), 4837-4845

CODEN: NARHAD; ISSN: 0305-1048

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous studies have established that a 32 bp cis-regulatory region, referred to as the H3core spanning -241 to -210 of the hamster histone H3.2 promoter, is critical for its G1/S-phase induction of transcription. Here the authors report that the transcription factor AP-2 is a major component of the protein complex which interacts with the H3core from hamster nuclear exts. In search of the control mechanism(s) whereby AP-2 can mediate cell cycle regulation of the histone H3.2 promoter, the authors found that AP-2 can phys. interact with the retinoblastoma (Rb) tumor suppressor protein in vitro, and when over-expressed, can also associate with Rb in vivo. Importantly, in contrast to the majority of Rb binding proteins, the C-terminal domain of Rb alone is sufficient for its interaction with AP-2. Using a reporter gene system linking tandem copies of the H3core to a heterologous minimal promoter, the authors demonstrated that over-expression of AP-2 proteins results in transactivation of the reporter gene through the H3core in a sequence-specific but orientation-independent manner. Addnl., this stimulative effect was suppressed by co-expression of Rb. Thus, AP-2, through its phys. and functional interaction with Rb, may contribute to the cell cycle regulation of its target genes.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:225669 HCAPLUS

DOCUMENT NUMBER: 126:221430

TITLE: Preponderance of Fis-binding sites in the R6K γ origin and the curious effect of the penicillin resistance marker on replication of this origin in the absence of Fis. [Erratum to document cited in CA125:187335]

AUTHOR(S): **Wu, Frank**; Wu, Jiazhen; Ehley, Jennifer; Filutowicz, Marcin

CORPORATE SOURCE: Dep. Bacteriol., Univ. Wisconsin, Madison, WI, 53706, USA

SOURCE: Journal of Bacteriology (1997), 179(7), 2464
CODEN: JOBAA; ISSN: 0021-9193

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The errors were not reflected in the abstract or the index entries.

L12 ANSWER 15 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:494603 HCAPLUS

DOCUMENT NUMBER: 125:187335

TITLE: Preponderance of Fis-binding sites in the R6K γ origin and the curious effect of the penicillin resistance marker on replication of this origin in the absence of Fis

AUTHOR(S): **Wu, Frank**; Wu, Jiazhen; Ehley, Jennifer; Filutowicz, Marcin

CORPORATE SOURCE: Dep. Bacteriol., Univ. Wisconsin, Madison, WI, 53706, USA

SOURCE: Journal of Bacteriology (1996), 178(16), 4965-4974
CODEN: JOBAA; ISSN: 0021-9193

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fis protein is shown here to bind to 10 sites in the γ origin of plasmid R6K. The Fis-binding sites overlap all the previously identified binding sites in the γ origin for the plasmid-encoded π initiator protein and three host-encoded proteins, DnaA, integration host factor, and RNA polymerase. However, the requirement of Fis for R6K replication depends on the use of copy-up π -protein variants and, oddly, the antibiotic resistance marker on the plasmid. In Fis-deficient cells, copy-up π variants cannot drive replication of R6K γ -origin plasmids carrying the bla gene encoding resistance to penicillin (Penr) but can drive replication of plasmids with the same origin but carrying the chloramphenicol acetyltransferase gene encoding chloramphenicol resistance (Cmr). In contrast, R6K replication driven by wild-type π is unaffected by the antibiotic resistance marker in the absence of Fis protein. Individually, none of these elements (copy-up π , Fis deficiency, or drug markers) prevents R6K replication. The replication defect is not caused by penicillin in the medium or runaway replication and is unaffected by the orientation of the bla gene relative to the origin. Replication remains inhibited when part of the bla coding segment is deleted but the bla promoter is left intact. However, replication is restored by insertion of transcriptional terminators on either side of the γ origin, suggesting that excess transcription from the bla gene may inactivate replication driven by π copy-up mutants in the absence of Fis. This study suggests that vector sequences such as drug markers may

not be inconsequential in replication studies, as is generally assumed.

L12 ANSWER 16 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:325931 HCAPLUS

DOCUMENT NUMBER: 125:2228

TITLE: Cell cycle arrest in G0/G1 phase by contact inhibition

and TGF- β 1 in mink Mv1Lu lung epithelial cells

AUTHOR(S): **Wu, Frank**; Buckley, Sue; Bui, Kim Chi; Yee,

Ann; Wu, Hua-Yang; Liu, Jian; Warburton, David

CORPORATE SOURCE: Dep. Surgery Pediatrics, Univ. Southern California

Sch. Med., Los Angeles, CA, 90027, USA

SOURCE: American Journal of Physiology (1996), 270(5, Pt. 1),
L879-L888

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We postulated that contact inhibition and transforming growth factor (TGF)- β 1 may target the same mols. to neg. regulate the Mv1Lu cell cycle in G0/G1. Both contact inhibition and TGF- β 1 suppressed the expression of a 45-kDa protein (p45); cyclins D2 and B1; cyclin-dependent protein kinase (Cdk)-4, Cdc-2, and Cdc-2-associated activity; and the phosphorylation of retinoblastoma tumor-suppressor protein (pRb) but did not affect the expression of cyclins D1, E, and A or the expression of Cdk-2 and Cdk-5. Expression of p45 reappeared 12 h after release from contact inhibition and 6-8 h after release from TGF- β 1, while TGF- β 1 prevented release from contact inhibition and maintained suppression of both p45 and cyclin D2. Addnl., cyclin D2 phosphorylation and its associated kinase activity were strongly inhibited by contact inhibition and TGF- β 1. Thus suppression of p45, cyclin D2/Cdk-4, and cyclin B1/Cdc-2 expression and/or activities is targeted both by contact inhibition and by TGF- β 1 and may define common mechanisms through which these neg. growth signals are integrated.

L12 ANSWER 17 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:66091 HCAPLUS

DOCUMENT NUMBER: 124:137134

TITLE: Structural and functional dissection of a DNA replication origin enhancer

AUTHOR(S): **Wu, Frank**

CORPORATE SOURCE: Univ. of Wisconsin, Madison, WI, USA

SOURCE: (1995) 218 pp. Avail.: Univ. Microfilms Int., Order
No. DA9537154

From: Diss. Abstr. Int., B 1995, 56(8), 4164

DOCUMENT TYPE: Dissertation

LANGUAGE: English

AB Unavailable

L12 ANSWER 18 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:936822 HCAPLUS

DOCUMENT NUMBER: 124:47153

TITLE: A DNA segment conferring stable maintenance on R6K γ -origin core replicons

AUTHOR(S): **Wu, Frank**; Levchenko, Igor; Filutowicz,
Marcin

CORPORATE SOURCE: Dep. Bacteriol., Univ. Wisconsin, Madison, WI, 53706,
USA

SOURCE: Journal of Bacteriology (1995), 177(22), 6338-45

CODEN: JOBAAAY; ISSN: 0021-9193

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The plasmid R6K γ origin consists of two adjacent modules, the enhancer and the core, and requires R6K initiator protein π for replication. While the core alone can replicate at a low level of wild-type π protein, the authors show here that host cells do not stably maintain core plasmids. The presence of the enhancer segment confers stable inheritance on core plasmids without a significant change in average plasmid copy number. Deletions and site-directed mutagenesis indicated that the stability of core plasmids is not mediated by binding sites or consensus sequences in the enhancer for DnaA, π protein, gyrase, Fis, or Dcm methylase. Proper segregation of core plasmids requires only the R6K stb or stability-related region, which includes the 20-bp segment of the 100-bp enhancer adjacent to the core. The use of the π 116 mutant protein, which increased plasmid copy 100-bp enhancer adjacent to the core. The use of the π 116 mutant protein, which increases plasmid copy number fourfold, does not stabilize core plasmids lacking the enhancer. The authors also show that at an elevated level of wild-type π , the γ -origin plasmid is unstable, even in the presence of the enhancer. The authors discuss the differences and similarities between the R6K stability system and those found in other plasmids.

L12 ANSWER 19 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:528192 HCAPLUS

DOCUMENT NUMBER: 122:308584

TITLE: Induction of A- and D-type cyclins and cdc2 kinase activity during recovery from short-term hyperoxic lung injury

AUTHOR(S): Bui, Kim Chi; Buckley, Sue; Wu, Frank; Uhal, Bruce; Joshi, Iravati; Liu, Jian; Hussain, Mukarram; Makhoul, Imad; Warburton, David

CORPORATE SOURCE: Div. Neonatology, Pediatric Pulmonology, Children's Hosp., Los Angeles, Los Angeles, CA, 90027, USA

SOURCE: American Journal of Physiology (1995), 268(4, Pt. 1), L625-L635

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hyperoxia causes a reproducible pattern of lung injury and repair in rodents, in which proliferation of alveolar epithelial cells (AEC) and fibroblasts is observed during recovery. We postulated that if cyclin expression and cyclin-dependent protein kinase activity would be reactivated in AEC during the repair process after hyperoxic lung injury. To test this hypothesis, we exposed adult rats to short-term hyperoxia, followed by recovery for various times in room air. Cellular proliferation in vivo was confirmed by (1) flow cytometric anal. of DNA content (FACS) of freshly isolated AEC and (2) immunohistochem. of proliferating cell nuclear antigen (PCNA) and bromodeoxy-uridine (BrdU) incorporation into DNA on lung sections. The percentage of freshly isolated AEC in S phase and G2/M phase on FACS anal. increased twofold to a maximum of 16.5%, after 48 h in 100% oxygen and 48 h recovery in air. Cyclins A and D and p34cdc2 protein expression were also increased during the recovery period, while p33cdk2 and p34cdk4 increased only slightly. P34cdc2 histone H1 kinase activity, both in whole lung and in AEC, decreased initially after 48 h in oxygen. However, a marked increase in p34cdc2 kinase activity was maximal at 24 h of recovery in air. We conclude that cyclins A and D and p34cdc2 protein expression and p34cdc2 kinase activity are increased in vivo during recovery from hyperoxic lung

injury in both adult rat lungs and in AEC isolated from these lungs. We speculate that the induction of cyclin-dependent protein kinase activity is a key event in mediating the proliferative cellular repair response to lung injury.

L12 ANSWER 20 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:454870 HCAPLUS
 DOCUMENT NUMBER: 122:262133
 TITLE: Differential expression of cyclin D2 and cdc2 genes in proliferating and nonproliferating alveolar epithelial cells
 AUTHOR(S): Wu, Frank; Buckley, Sue; Bui, Kim Chi; Warburton, David
 CORPORATE SOURCE: Dep. of Pediatrics, Univ. of Southern California School of Medicine, Los Angeles, CA, USA
 SOURCE: American Journal of Respiratory Cell and Molecular Biology (1995), 12(1), 95-103
 CODEN: AJRBEL; ISSN: 1044-1549
 PUBLISHER: American Lung Association
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Alveolar epithelial cells (AEC) proliferate during embryonic and fetal life, while in the adult lung AEC form a highly differentiated population that does not usually divide. Herein, the authors tested the hypothesis that differential expression of specific cell cycle control genes may occur during AEC development and transformation. The authors compared normal rat AEC in primary culture with transformed AEC for the expression of D-type G1 cyclins and cyclin-dependent protein kinases (cdc2 and cdk2). Cyclin D1 mRNA and protein were expressed at comparable levels in both normal rat AEC and in transformed AEC. In contrast, high levels of cyclin D2 mRNA and protein expression were only observed in normal 19-day fetal rat AEC and in transformed mink mV1Lu cells derived from fetal mink lung epithelium. Moreover, treatment either with antisense oligodeoxynucleotides directed against cyclin D2 mRNA or with genistein (a tyrosine kinase inhibitor) caused significant inhibition of [³H]thymidine incorporation into DNA as well as inhibition of cyclin D2 expression in normal 19-day fetal rat AEC. P34cdc2 (but not p33cdk2 or p34cdk4) was expressed at progressively decreasing levels with corresponding histone H1 kinase activities during rat AEC development (19-day fetal > 21-day fetal > 13-day postnatal > adult rat AEC). The levels of p34cdc2 histone H1 kinase activity were significantly up-regulated or amplified in adult rat type 2 AEC following hyperoxic injury and repair and in transformed AEC. Collectively, these data support an important functional role for cyclin D2 and cdc2 genes in determining the proliferative vs. nonproliferative phenotype of AEC during lung development, injury and repair, and transformation.

L12 ANSWER 21 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:213230 HCAPLUS
 DOCUMENT NUMBER: 122:25257
 TITLE: Binding of DnaA protein to a replication enhancer counteracts the inhibition of plasmid R6K γ origin replication mediated by elevated levels of R6K π protein
 AUTHOR(S): Wu, Frank; Levchenko, Igor; Filutowicz, Marcin
 CORPORATE SOURCE: Dep. Bacteriol., Univ. Wisconsin, Madison, WI, 53706, USA
 SOURCE: Journal of Bacteriology (1994), 176(22), 6795-801
 CODEN: JOBAAY; ISSN: 0021-9193

PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Replication of the γ origin of Escherichia coli plasmid R6K requires π protein, encoded by the R6K pir gene, and many host factors, including DnaA protein. π Has dual roles, activating replication at low levels and inhibiting replication at high levels. The inhibitory function of π is counteracted by integration host factor and a specific sequence of the origin called the enhancer. This 106-bp DAN segment contains a binding site for DnaA protein (DnaA box 1). In this study, we mutated this site to determine if it was required for the enhancer's function. Using γ origin derivative plasmids with the DnaA box 1 altered or deleted, we show that this site is necessary to protein the origin against levels of wild-type π protein that would otherwise inhibit replication. To show that the base substitutions in DnaA box 1 weakened the binding of DnaA, we developed a new application of the agarose gel retardation assay. This quick and easy assay has broad applicability, as shown in binding studies with DNA fragments carrying a different segment of the R6K origin, the chromosomal origin (oriC), or the pUC origin. The gel retardation assay suggests a stoichiometry of DnaA binding different from that deduced from other assays.

L12 ANSWER 22 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:211219 HCAPLUS

DOCUMENT NUMBER: 122:56390

TITLE: Synthesis of (+)-6-amino-9-[5-(hydroxymethyl)-1,3-dioxolan-2-yl]purine for anti-HIV activity investigation

AUTHOR(S): Wu, Frank; Hsu, Shih-Yuan; Chen, Chieh-Fu

CORPORATE SOURCE: National Research Institute Chinese Medicine, Taipei, Taiwan

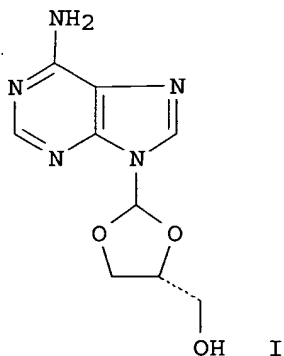
SOURCE: Chinese Pharmaceutical Journal (Taipei, Taiwan) (1994), 46(3), 245-8

CODEN: CPHJEP; ISSN: 1016-1015

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB The title compound [namely, (+)-2-(6-amino-9H-purin-9-yl)-1,3-dioxolane-4-methanol] (I) was prepared from (+)-solketal. Data for antiviral activity of I (anti-HIV activity) were not reported.

L12 ANSWER 23 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:186472 HCAPLUS
 DOCUMENT NUMBER: 122:97559
 TITLE: Regulation of replication of an iteron-containing DNA molecule
 AUTHOR(S): Filutowicz, Marcin; Dellis, Stephanie; Levchenko, Igor; Urh, Marjeta; Wu, Frank; York, Dona
 CORPORATE SOURCE: Department Bacteriology, University Wisconsin, Madison, WI, 53706, USA
 SOURCE: Progress in Nucleic Acid Research and Molecular Biology (1994), 48, 239-73
 CODEN: PNMBAF; ISSN: 0079-6603
 PUBLISHER: Academic
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 234 refs.

L12 ANSWER 24 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:406267 HCAPLUS
 DOCUMENT NUMBER: 121:6267
 TITLE: Cell cycle-dependent expression of cyclin D1 and a 45 kD protein in human A549 lung carcinoma cells
 AUTHOR(S): Wu, Frank; Bui, Kim Chi; Buckley, Sue; Warburton, David
 CORPORATE SOURCE: Div. Neonatol. Pediatric Pulmonol., Child. Hosp. Los Angeles, Los Angeles, CA, USA
 SOURCE: American Journal of Respiratory Cell and Molecular Biology (1994), 10(4), 437-47
 CODEN: AJRBEL; ISSN: 1044-1549
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Cyclin D1, which is suggested to have a role in G1 control during the cell cycle, is genetically linked to BCL-1 and is widely overexpressed in parathyroid, breast, and squamous cancer cells. The authors postulated that cyclin D1 regulation may also be important in lung cancer. Therefore, the authors characterized the cell cycle-dependent expression of cyclin D1 at both mRNA and protein levels in synchronized human A549 lung carcinoma cells. Monospecific anti-cyclin D1 C-terminal peptide antibodies recognized both p36cyclinD1 and an as-yet uncharacterized 45 kD protein (p45). A549 cells were synchronized with well-studied drugs. Cyclin D1 mRNA expression remained relatively constant, with less than a twofold fluctuation during the cell cycle and with a minor peak at M phase. However, the p36cyclinD1 protein fluctuated during the A549 cell cycle and was expressed at very low levels in late G1 and at the G1/S boundary, but then increased in S phase and peaked at M phase. In contrast, p45 protein was expressed at relatively high levels in late G1 and reached maximal levels at the G1/S boundary, was expressed at decreased levels in S phase, and then had disappeared by M phase. Moreover, p45 was highly expressed only in transformed alveolar epithelial cells, but not in normal rat alveolar epithelial cells or fetal rat lung fibroblasts in primary cultures. In mink Mv1Lu cells, the expression of p45 was totally blocked by transforming growth factor- β 1 treatment or contact inhibition. P45 protein was phosphorylated on serine, threonine, and tyrosine residues in A549 cells in culture. The phosphorylation of the p45 protein was cell cycle-regulated and reached its maximal levels at G2/M phase. The p45 protein had a different peptide map from p36cyclinD1 after cleavage with N-chlorosuccinimide. Immunopptn. studies showed that p45 was also anti-ubiquitin immunoreactive during the cell cycle. The authors conclude that p36cyclinD1 and the p45 protein are differentially regulated in a cell cycle-dependent manner in A549 cells. Although p45 is antigenically related to p36cyclinD1, it is probably not a closely

cyclin-related protein. The authors speculate that p45 may be associated with malignant transformation and may play a distinct role from p36cyclinD1 in regulation of the cell cycle in A549 cells.

L12 ANSWER 25 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:160230 HCAPLUS

DOCUMENT NUMBER: 120:160230

TITLE: Cyclin A expression in normal and transformed alveolar epithelial cells

AUTHOR(S): Bui, Kim Chi; Wu, Frank; Buckley, Susan; Wu, Lingtao; Williams, Richard; Carbonaro-Hall, Denise; Hall, Frederick L.; Warburton, David

CORPORATE SOURCE: Dep. Pediatr., Child. Hosp. Los Angeles, Los Angeles, CA, 90027, USA

SOURCE: American Journal of Respiratory Cell and Molecular Biology (1993), 9(2), 115-25
CODEN: AJRBEL; ISSN: 1044-1549

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mature adult alveolar epithelial cell (AEC) is a highly differentiated phenotype that does not readily divide and exhibits numerous specialized functions. Yet, transformed AEC proliferate aggressively in certain forms of lung cancer. Normal AEC also proliferate but in a coordinated manner during embryonic growth and fetal development as well as during lung repair. Therefore, biochem. mechanisms regulating the cell cycle in AEC are clearly of fundamental significance for understanding lung development, lung injury, and cancer. Cyclin A is a protein that varies in abundance during the cell cycle and regulates critical transition points through its association with cyclin-dependent protein kinase subunits. The authors postulated that high expression of cyclin A might be associated with rapid proliferation in transformed AEC. The authors compared the expression of cyclin A mRNA and protein in primary cultures of fetal and adult rat AEC, in the E1A-T2 neonatal rat AEC, and in the malignant A549 human AEC. The authors used pharmacol. blockades with mimosine, aphidicolin, and nocodazole for cell cycle synchronization, which was verified by fluorescence-activated cell sorter (FACS) anal. of cellular DNA content. Transformed cells (A549 and E1A-T2) exhibited a much higher level of expression for both cyclin A mRNA and protein than did normal rat AEC. Induction of cyclin A mRNA expression in A549 human AEC and E1A-T2 rat AEC occurred in late G1, prior to the onset of S phase. Fetal and adult rat AEC and rat E1A-T2 AEC expressed two cyclin A mRNA transcripts, whereas human A549 cells in S phase and M phase expressed three cyclin A mRNA transcripts. The authors conclude that transformed AEC overexpress cyclin A in comparison with primary AEC cultures, while retaining cell cycle-dependent differences in cyclin A expression. The authors speculate that cyclin A expression is regulated both at the transcriptional and post-transcriptional levels, and that cyclin A may play a key role in the increased proliferation of transformed AEC that is associated with the pathogenesis of lung cancer.

L12 ANSWER 26 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:574747 HCAPLUS

DOCUMENT NUMBER: 119:174747

TITLE: Identification of a human epidermal growth factor receptor-associated protein kinase as a new member of the mitogen-activated protein kinase/extracellular signal-regulated protein kinase family

AUTHOR(S): Williams, Richard; Sanghera, Jasbinder; Wu, Frank; Carbonaro-Hall, Denise; Campbell, Donna L.; Warburton, David; Pelech, Steven; Hall, Frederick

CORPORATE SOURCE: Div. Orthop. Surg., Child. Hosp., Los Angeles, CA, USA
 SOURCE: Journal of Biological Chemistry (1993), 268(24),
 18213-17
 CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A putative mitogen-activated protein kinase (MAPK) has recently been identified, which potentially phosphorylates the human epidermal growth factor (EGF) receptor at a physiol. site (Thr-669) and is distinguished from other MAPKs/extracellular signal-regulated protein kinases (ERKs) on the basis of chromatog., immunol., and kinetic data. Here the authors report that this newly discovered MAPK is phys. associated with the EGF receptor in A431 cells and with the related receptor/tyrosine kinase HER2 (encoded by c-neu) in enzyme preps. obtained from Wilm's tumors. This human EGF receptor-associated kinase is characterized as a 40-kDa Thr-669 kinase that exists in a high mol. mass complex with the resp. growth factor receptor. EGF treatment of A431 cells stimulates the tyrosine phosphorylation of p40 and increases Thr-669 kinase activity in p40-containing fractions. The 40-kDa kinase is recognized by affinity-purified polyclonal antibodies directed against the sea star p44mpk and a Pan-ERK antibody directed against the conserved subdomain VIII of MAPKs/ERKs, but is not recognized by antibodies selective for the rat p44erk1 and/or the p42mapk/erk2 isoforms, thus identifying the EGF receptor-associated kinase as a novel MAPK that may regulate receptor function in vivo.

L12 ANSWER 27 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:552729 HCAPLUS

DOCUMENT NUMBER: 119:152729

TITLE: Role of epidermal growth factor expression in early mouse embryo lung branching morphogenesis in culture: antisense oligodeoxynucleotide inhibitory strategy

AUTHOR(S): Seth, Rajeev; Shum, Lillian; Wu, Frank; Wuenschell, Carol; Hall, Frederick L.; Slavkin, Harold C.; Warburton, David

CORPORATE SOURCE: Child. Hosp. Los Angeles, Univ. Southern California, Los Angeles, CA, 90027, USA

SOURCE: Developmental Biology (Orlando, FL, United States) (1993), 158(2), 555-9
 CODEN: DEBIAO; ISSN: 0012-1606

DOCUMENT TYPE: Journal

LANGUAGE: English

AB EGF expression and branching morphogenesis were inhibited using a 5' 15-mer antisense oligodeoxynucleotide (ODN) directed against EGF precursor mRNA in embryonic mouse lung in culture under chemical defined, serumless conditions. Antisense EGF ODN resulted in >90% inhibition of EGF immunoreactive peptide synthesis, 75% reduction in branching morphogenesis, 73% decrease in DNA content, 64% decrease in RNA content, 73% decrease in protein synthesis, and 65% decrease in [3H]thymidine incorporation into DNA compared to Embryonic Day 11 controls in culture for 4 days. Sense ODN results were similar to control. Supplementing antisense ODN with EGF partially reversed antisense effects. The results further support a role for EGF in pulmonary organogenesis.

L12 ANSWER 28 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:446504 HCAPLUS

DOCUMENT NUMBER: 119:46504

TITLE: Two potentially oncogenic cyclins, cyclin A and cyclin D1, share common properties of subunit configuration, tyrosine phosphorylation and physical association with the Rb protein

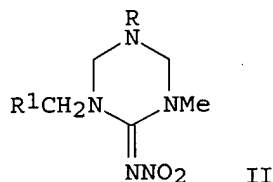
AUTHOR(S): Hall, Frederick L.; Williams, Richard T.; Wu, Lingtao;
Wu, Frank; Carbonaro-Hall, Denise A.; Harper,
 J. Wade; Warburton, David
 CORPORATE SOURCE: Div. Orthop. Surg., Child. Hosp. Los Angeles, Los
 Angeles, CA, 90054-0700, USA
 SOURCE: Oncogene (1993), 8(5), 1377-84
 CODEN: ONCNES; ISSN: 0950-9232
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Originally identified as a mitotic cyclin, cyclin A exhibits properties of growth factor sensitivity, susceptibility to viral subversion, and association with a tumor-suppressor protein; these properties are indicative of an S-phase-promoting factor (SPF) as well as a candidate protooncogene. Human cyclin D1 (PRAD1) was also identified as a putative G1 cyclin and candidate protooncogene. The coordinate interactions between the 2 potentially oncogenic cyclins, cyclin-dependent protein kinase subunits (cdks) and the Rb tumor-suppressor protein, were studied. The distribution of cyclin D isoforms was modulated by serum factors in primary fetal rat lung epithelial cells. Cyclin D1 was phosphorylated on tyrosine residues in vivo and, like cyclin A, was readily phosphorylated by pp60c-src in vitro. In synchronized human osteosarcoma cells, cyclin D1 was induced in early G1 and became associated with p9Ckshs1, a Cdk-binding subunit. Immunopptn. expts. with human osteosarcoma cells and Ewing sarcoma cells demonstrated that cyclin D1 was associated with both p34cdc2 and p33cdk2, and that cyclin D1 immune complexes exhibited appreciable histone H1 kinase activity. Immobilized recombinant cyclins A and D1 associated with cellular proteins in complexes that contained the p105Rb protein. Tyrosine phosphorylation and the potential to interact directly or indirectly with the Rb protein may be related to the membrane-mediated signaling events in the regulation of gene expression.

L12 ANSWER 29 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:235455 HCAPLUS
 DOCUMENT NUMBER: 116:235455
 TITLE: Preparation of substituted nitroguanidines as
 insecticides
 INVENTOR(S): **Wu, Frank**; Katsurayama, Takayoshi; Segami,
 Shigenori; Takasuka, Seiji
 PATENT ASSIGNEE(S): Agro-Kanesho Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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JP 03291267	A2	19911220	JP 1990-91237	19900405
JP 06074249	B4	19940921		
PRIORITY APPLN. INFO.:			JP 1990-91237	19900405
OTHER SOURCE(S):			CASREACT 116:235455; MARPAT 116:235455	
GI				



AB R1CH2NHC(:NNO2)NHMe (I; R1 = 2-chloro-5-pyridyl or 2-chloro-5-thiazoyl), useful as insecticides (no data), are prepared by ring cleavage of hexahydrotriazines II (R = lower alkyl, alkenyl) in presence of acids. A solution of 0.5 g II (R = Me, R1 = 2-chloro-5-pyridyl) in AcOH was treated with HCl at 50-60° for 30 min to give I.

L12 ANSWER 30 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:189083 HCAPLUS

DOCUMENT NUMBER: 116:189083

TITLE: Roles of a 106-bp origin enhancer and Escherichia coli DnaA protein in replication of plasmid R6K

AUTHOR(S): Wu, Frank; Goldberg, Ilya; Filutowicz, Marcin

CORPORATE SOURCE: Dep. Bacteriol., Univ. Wisconsin, Madison, WI, 53706, USA

SOURCE: Nucleic Acids Research (1992), 20(4), 811-17

CODEN: NARHAD; ISSN: 0305-1048

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A dnaA null strain could not support replication of intact plasmid R6K or derivs. containing combinations of its three replication origins (α , γ , β). dnaA Binds in vitro to sites in two functionally distinct segments of the central γ origin. The 277-bp core segment is common to all three origins and contains DnaA box 2, which cannot be deleted without preventing replication. Immediately to the left of the core lies the 106-bp origin enhancer, which contains DnaA box 1. When the origin enhancer is deleted, the core alone can still initiate replication if levels of wt π protein are decreased or if copy-up π mutant proteins are provided in trans. dnaA Does not effect expression of R6K replication initiator protein π , although several DnaA boxes were identified in the coding segment of the pir gene, which encodes π . Together these data suggest that a single DnaA box 2, is sufficient for initiation from the γ origin and might be sufficient and required for the activity of the α and β origins as well. Implications of the DnaA protein binding to two domains of the γ origin and the role of the 106-bp origin enhancer in replication are discussed.

L12 ANSWER 31 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:123318 HCAPLUS

DOCUMENT NUMBER: 116:123318

TITLE: Preparation of tetrahydropyrimidines as insecticides.

INVENTOR(S): Wu, Frank; Kariya, Akinori; Kumada, Hiroko; Sato, Junko; Nanjo, Katsumi; Segami, Shigenori; Takasuka, Seiji; Henmi, Shinya; Tsuji, Atsushi; et al.

PATENT ASSIGNEE(S): Agro-Kanesho Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.

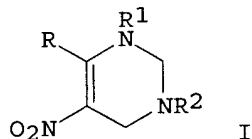
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03264580	A2	19911125	JP 1990-61885	19900313
PRIORITY APPLN. INFO.:			JP 1990-61885	19900313
OTHER SOURCE(S):	MARPAT	116:123318		
GI				



AB Insecticides contain the title compds. I (R = NHCH₂Y; R₁ = lower alkyl; R₂ = R₁, alkenyl, cycloalkyl, aralkyl, haloalkyl; Y = 2-chloro-5-pyridyl, 2-chloro-5-thiazolyl), prepared from I (R = SR₃; R₃ = lower alkyl) and YCH₂NH₂. A mixture of 2.0 g I (R = SMe, R₁ = R₂ = Me) and 2.2 g 2-chloro-5-pyridylmethylamine in iso-Pr alc. was refluxed for 5 h to give 3.2 g I (R = 2-chloro-5-pyridylmethylamino, R₁ = R₂ = Me), which (at 500 ppm) controlled *Nephotettix cincticeps* on rice with 100% mortality, vs. 70%, for sumithion.

L12 ANSWER 32 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:583374 HCAPLUS

DOCUMENT NUMBER: 115:183374

TITLE: Preparation of hexahydrotriazine compounds as insecticides

INVENTOR(S): Wu, Frank; Kariya, Akinori; Katsuyama, Noriyoshi; Tsuji, Atsushi; Takasuka, Kiyoshi; Segami, Shigenori; Nanjo, Katsumi; Sato, Junko

PATENT ASSIGNEE(S): Agro-Kanesho Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 428941	A1	19910529	EP 1990-121383	19901108
EP 428941	B1	19950503		
R: CH, DE, FR, GB, IT, LI				
JP 03218370	A2	19910925	JP 1990-24199	19900202
JP 06000776	B4	19940105		
AU 9065623	A1	19910516	AU 1990-65623	19901031
AU 628229	B2	19920910		
US 6187773	B1	20010213	US 1990-606848	19901031
KR 147056	B1	19980817	KR 1990-18143	19901109
CN 1060656	A	19920429	CN 1990-109039	19901110
CN 1026648	B	19941123		
CN 1098719	A	19950215	CN 1994-103331	19940325
CN 1050600	B	20000322		
US 2001046994	A1	20011129	US 2000-729865	20001206

PRIORITY APPLN. INFO.:

JP 1989-292675

A 19891110

JP 1990-24199

A 19900202

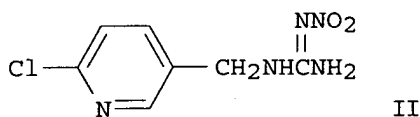
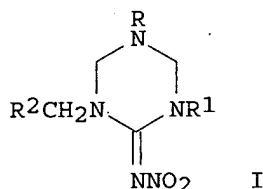
US 1990-606848

A3 19901031

OTHER SOURCE(S):

MARPAT 115:183374

GI



AB Hexahydrotriazine derivs. [I; R = alkyl, alkenyl; R1 = H, alkyl, alkenyl, alkynyl, (6-chloro-3-pyridyl)methyl; R2 = 6-chloro-3-pyridyl, 2-chlorothiazol-5-yl] are prepared. A solution of Et3N in THF was added to a suspension of 0.6 g guanidine derivative II and 0.4 g (ClCH2)2NMe in THF with stirring under cooling to give 0.78 g I (R = Me, R1 = H, R2 = 6-chloro-3-pyridyl), which killed 100% green rice leafhopper larvae at 500 ppm. Also prepared and tested were 11 addnl. I.

L12 ANSWER 33 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1987:119679 HCAPLUS

DOCUMENT NUMBER: 106:119679

TITLE: Heterocyclic esters of phenoxybenzoic acids useful as herbicides

INVENTOR(S): Wu, Frank

PATENT ASSIGNEE(S): Sandoz A.-G., Switz.

SOURCE: U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 475,414, abandoned.

CODEN: USXXAM

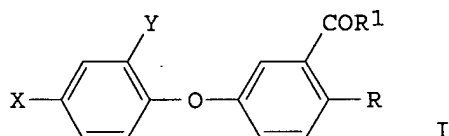
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4618359	A	19861021	US 1985-715442	19850325
PRIORITY APPLN. INFO.:			US 1982-351697	A2 19820224
			US 1983-475414	A2 19830314
OTHER SOURCE(S):		CASREACT 106:119679; MARPAT 106:119679		
GI				



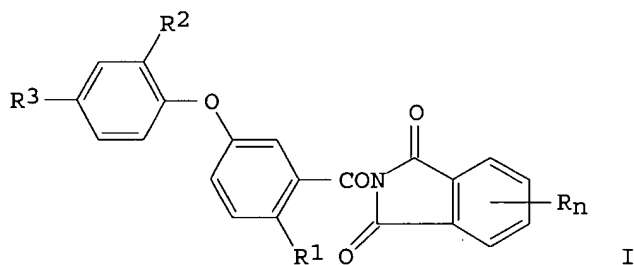
AB Title compds. I (X = F3C; Y = H, halo, O2N, NC; R = O2N, alkylthio, halo, NC; R1 = tetrahydrofuryloxy) were prepared by esterification of I (R1 = Cl) with hydroxytetrahydrofuran. Thus, 2-nitro-5-(2-chloro-4-

trifluoromethylphenoxy)benzoic acid was converted with SOCl₂ to I (X = F₃C, Y = Cl, R = O₂N, R₁ = Cl) which was stirred with 3-hydroxytetrahydrofuran and Et₃N to give I (X = F₃C, Y = Cl, R = O₂N, R₁ = 3-tetrahydrofuryloxy) (II). In postemergence screen in the greenhouse, II at 0.125 lb/acre gave complete control of alfalfa and wild mustard. A dust formulation contained II 10, talc 90 parts.

L12 ANSWER 34 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1984:138777 HCAPLUS
 DOCUMENT NUMBER: 100:138777
 TITLE: Phthalimides of phenoxybenzoic acids
 INVENTOR(S): Wu, Frank; Stach, Leonard J.
 PATENT ASSIGNEE(S): Velsicol Chemical Corp. , USA
 SOURCE: U.S., 7 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4427441	A	19840124	US 1982-410679	19820823
PRIORITY APPLN. INFO.:			US 1982-410679	19820823
OTHER SOURCE(S):		CASREACT 100:138777; MARPAT 100:138777		
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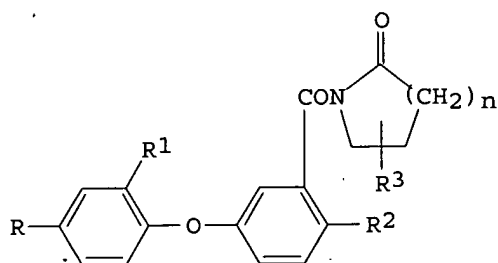
AB Benzamides I (R = alkyl, Cl, Br, NO₂; n = 0, 1, 2, 3, 4; R₁ = NO₂, alkylthio, Cl, Br, cyano; R₂ = H, Cl, Br, NO₂, cyano; R₃ = Cl, Br, CF₃) were prepared from benzoyl chlorides and phthalimide K salts. 2-Nitro-5-(4-trifluoromethyl-2-chlorophenoxy)benzoyl chloride was treated with phthalimide K salt to give I (n = 0, R₁ = NO₂, R₂ = Cl, R₃ = CF₃), which exhibited herbicidal activity.

L12 ANSWER 35 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1983:594824 HCAPLUS
 DOCUMENT NUMBER: 99:194824
 TITLE: N-Acylated lactams, their herbicidal compositions and use
 INVENTOR(S): Stach, Leonard J.; Wu, Frank
 PATENT ASSIGNEE(S): Velsicol Chemical Corp. , USA
 SOURCE: U.S., 6 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent

LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4398938	A	19830816	US 1982-379839	19820520
CA 1184909	A1	19850402	CA 1983-425523	19830408
IN 159562	A	19870523	IN 1983-DE263	19830421
GB 2120658	A1	19831207	GB 1983-10915	19830422
GB 2120658	B2	19860219		
IL 68474	A1	19860331	IL 1983-68474	19830422
ZA 8302936	A	19840125	ZA 1983-2936	19830426
NL 8301522	A	19831216	NL 1983-1522	19830429
CH 653672	A	19860115	CH 1983-2332	19830429
BR 8302563	A	19840117	BR 1983-2563	19830516
DE 3317936	A1	19831124	DE 1983-3317936	19830517
BE 896780	A1	19830916	BE 1983-210799	19830518
DK 8302245	A	19831121	DK 1983-2245	19830519
NO 8301774	A	19831121	NO 1983-1774	19830519
SE 8302824	A	19831121	SE 1983-2824	19830519
FR 2527207	A1	19831125	FR 1983-8291	19830519
FR 2527207	B1	19871224		
ES 522546	A1	19840916	ES 1983-522546	19830519
HU 32992	O	19841029	HU 1983-1773	19830519
HU 190633	B	19860929		
SU 1209018	A3	19860130	SU 1983-3631051	19830519
AT 8301834	A	19860715	AT 1983-1834	19830519
AT 382290	B	19870210		
AU 8314822	A1	19831124	AU 1983-14822	19830520
AU 553790	B2	19860724		
JP 58210062	A2	19831207	JP 1983-89046	19830520
DD 209714	A5	19840523	DD 1983-251133	19830520
			US 1982-379839	A 19820520
PRIORITY APPLN. INFO.:			CASREACT 99:194824; MARPAT 99:194824	
OTHER SOURCE(S):				
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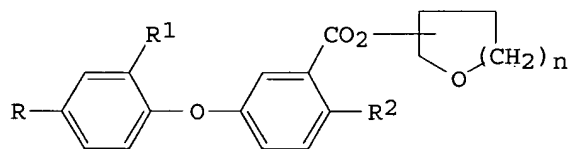


AB The amides I (R = halogen, CF₃; R₁ = H, halogen, cyano; R₂ = halogen, cyano, NO₂; R₃ = H, alkyl; n = 1-3) were prepared. Thus I (R = CF₃, R₁ = Cl, R₂ = NO₂, R₃ = H, n = 3, II) was obtained by acylating caprolactam. At 1 lb/acre post-emergence II was totally effective against a number of weeds.

L12 ANSWER 36 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1983:522277 HCAPLUS
 DOCUMENT NUMBER: 99:122277
 TITLE: Tetrahydrofuryl phenoxybenzoates
 INVENTOR(S): Wu, Frank

PATENT ASSIGNEE(S): Velsicol Chemical Corp. , USA
 SOURCE: Belg., 29 pp.
 CODEN: BEXXAL
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 895662	A1	19830516	BE 1983-209940	19830120
IL 67513	A1	19860228	IL 1982-67513	19821217
IN 159369	A	19870509	IN 1982-DE924	19821217
AU 8291665	A1	19830901	AU 1982-91665	19821220
AU 556105	B2	19861023		
ZA 8300146	A	19831026	ZA 1983-146	19830110
NL 8300084	A	19830916	NL 1983-84	19830111
FR 2521996	A1	19830826	FR 1983-779	19830119
FR 2521996	B1	19860905		
CA 1175849	A1	19841009	CA 1983-419935	19830120
BR 8300459	A	19831101	BR 1983-459	19830131
CH 653678	A	19860115	CH 1983-793	19830211
AT 8300581	A	19860715	AT 1983-581	19830221
AT 382292	B	19870210		
RO 85315	P	19840929	RO 1983-110112	19830222
RO 88222	B3	19851230	RO 1983-114628	19830222
DK 8300828	A	19830825	DK 1983-828	19830223
JP 58157778	A2	19830919	JP 1983-29202	19830223
DE 3306339	A1	19830922	DE 1983-3306339	19830223
ES 520010	A1	19840401	ES 1983-520010	19830223
GB 2115418	A1	19830907	GB 1983-5099	19830224
GB 2115418	B2	19860508		
PRIORITY APPLN. INFO.: GI			US 1982-351697	A 19820224

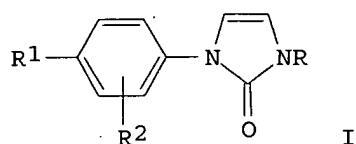


AB 3-Phenoxybenzoyl chlorides were converted to esters I (R = halo, CF₃; R₁ = H, halo, NO₂, cyano; R₂ = NO₂ alkylthio, halo, cyano; n = 1, 2; I [n = 1 (3-isomer), R = CF₃, R₁ = Cl, R₂ = NO₂] (II) exhibited herbicidal activity while other I were not tested. 2-Nitro-5-(4-trifluoromethyl-1,2-chlorophenoxy)benzoyl chloride was stirred with 3-hydroxytetrahydrofuran and Et₃N to give II.

L12 ANSWER 37 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1981:569187 HCAPLUS
 DOCUMENT NUMBER: 95:169187
 TITLE: Herbicidal N-substituted 4-imidazolin-2-ones
 INVENTOR(S): Wu, Frank
 PATENT ASSIGNEE(S): Velsicol Chemical Corp. , USA
 SOURCE: U.S., 13 pp. Cont.-in-part of U.S. Ser. No. 52,525, abandoned.
 CODEN: USXXAM

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

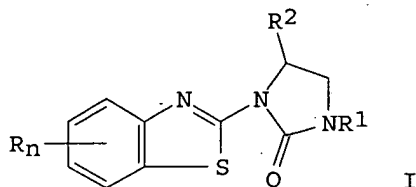
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4279637	A	19810721	US 1980-154185	19800529
PRIORITY APPLN. INFO.:			US 1979-52525	A2 19790602
OTHER SOURCE(S):	CASREACT 95:169187			
GI				



AB Imidazolinones I (R = H, alkyl; R1 = optionally substituted PhO, PhS, PhSO, PhSO2, PhCH2; R2 = H, halogen, trihaloalkyl, NO2, cyano, alkyl, alkoxy, alkylthio) were prepared. Thus, 4-PhOC6H4NH2 was treated with ClCO2Et and the carbamate treated with (MeO)2CHCH2NHMe to give 4-PhOC6H4NHCONMeCH2CH(OMe)2 which was cyclized with concentrated HCl to give I (R = Me, R1 = PhO, R2 = H). At 8 lb/acre post-emergence I (R = Me, R1 = PhO, R2 = H) gave total control of e.g. jimsonweed or velvetleaf.

L12 ANSWER 38 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1980:446667 HCAPLUS
 DOCUMENT NUMBER: 93:46667
 TITLE: 1-(Benzothiazolyl)imidazolidinones, their preparation and use
 INVENTOR(S): Wu, Frank; Krenzer, John
 PATENT ASSIGNEE(S): Velsicol Chemical Corp., USA
 SOURCE: Brit., 12 pp.
 CODEN: BRXXAA
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 1555619	A	19791114	GB 1977-21032	19770519
PRIORITY APPLN. INFO.:			GB 1977-21032	A 19770519
GI				



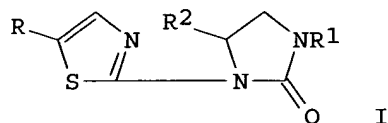
AB The title compds. I [R = alkyl, halo, haloalkyl, alkoxy; n = 0, 1, 2; R1 = alkyl, alkenyl, haloalkyl, HC.tplbond.CCR3R4 (R3, R4 = H, alkyl); R2 = OH, NR5R6 [R5, R6 = H, alkyl, alkenyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, (R7)mC6H5-m(CH2)x (m = 0, 1-3; x = 0, 1; R7 = alkyl, alkoxy, alkylthio, halo, haloalkyl, NO2, CN)], O2CR8 [R8 = alkyl, alkenyl, haloalkyl, alkynyl, alkoxyalkyl, cycloalkyl, (R7)mC6H5-m(CH2)x (R7, m, x as before)]] were prepared Thus, I (R = H, R1 = Me, R2 = OH) was prepared from 2-aminobenzothiazole by sequential treatment with COCl2 in AcOEt (reflux, 1 h), MeNHCH2CH(OMe)2 in C6H6 (room temperature, 1 h), and aqueous HCl-MeOH (N2, reflux, .apprx.15 min). I are useful as herbicides; their activities were assessed against a variety of weeds using pre- and postemergence testing.

L12 ANSWER 39 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1978:105336 HCAPLUS
 DOCUMENT NUMBER: 88:105336
 TITLE: 1-Thiazolyylimidazolidinones
 INVENTOR(S): Wu, Frank; Krenzer, John
 PATENT ASSIGNEE(S): Velsicol Chemical Corp., USA
 SOURCE: Ger. Offen., 36 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2724614	A1	19771215	DE 1977-2724614	19770601
US 4116969	A	19780926	US 1976-691743	19760601
US 4118390	A	19781003	US 1976-691949	19760601
CA 1078391	A1	19800527	CA 1977-278390	19770513
IL 52091	A1	19800731	IL 1977-52091	19770513
JP 52148072	A2	19771208	JP 1977-63152	19770530
JP 61034434	B4	19860807		
BE 855285	A1	19771003	BE 1977-178104	19770601
NL 7705992	A	19771205	NL 1977-5992	19770601
FR 2353548	A1	19771230	FR 1977-16735	19770601
FR 2353548	B1	19840302		
BR 7703562	A	19780228	BR 1977-3562	19770601
AU 7725729	A1	19781207	AU 1977-25729	19770601
AT 7703884	A	19790615	AT 1977-3884	19770601
AT 354442	B	19790110		
GB 1579771	A	19801126	GB 1977-23189	19770601
CH 634201	A	19830131	CH 1977-6733	19770601
PRIORITY APPLN. INFO.:			US 1976-691743	A 19760601
			US 1976-691941	A 19760601
			US 1976-691949	A 19760601

GI



AB The thiazolyylimidazolidinones I (R = halo, alkylsulfonyl; R1 = alkyl, alkenyl, alkynyl; R2 = OH, substituted or unsubstituted NH2, acyloxy) were prepared for use as herbicides. Thus, 5-bromo-2-thiazolyl isocyanate dimer was treated with MeNHCH2CH(OMe)2, followed by cyclization with HCl-MeOH to give I (R = Br, R1 = Me, R2 = OH) (II), which reacted with EtNH2 to give I (R = Br, R1 = Me, R2 = EtNH). Application of 1 lb/acre II solution gave complete destruction of Avena sativa.

L12 ANSWER 40 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1973:21477 HCAPLUS

DOCUMENT NUMBER: 78:21477

TITLE: Measurement of electron distribution function in a cesium plasma

AUTHOR(S): Chen, Che Jen; Wu, James; Wu, Frank

CORPORATE SOURCE: Jet Propul. Lab., Pasadena, CA, USA

SOURCE: Journal of Applied Physics (1972), 43(11), 4570-3

CODEN: JAPIAU; ISSN: 0021-8979

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A conventional plane Langmuir probe with d.c. superimposed on a small sinusoidal signal was used to measure the electron-energy distribution in a Cs discharge tube. The current-voltage characteristic and its 2nd-derivative characteristic are obtained for various discharge conditions. The electron-energy distribution at different-gas particle ds. and elec. fields in the pos. column are calculated. Deviation from a Maxwellian distribution is observed for a low-gas-d. and high-elec.-field plasma. The calcn. of the distribution function is also carried out by solving numerically elastic and inelastic collisions.

L12 ANSWER 41 OF 41 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1972:80788 HCAPLUS

DOCUMENT NUMBER: 76:80788

TITLE: Raman scattering cross section for dinitrogen tetroxide

AUTHOR(S): Chen, Che Jen; Wu, Frank

CORPORATE SOURCE: Jet Propul. Lab., Pasadena, CA, USA

SOURCE: Applied Physics Letters (1971), 19(11), 452-3

CODEN: APPLAB; ISSN: 0003-6951

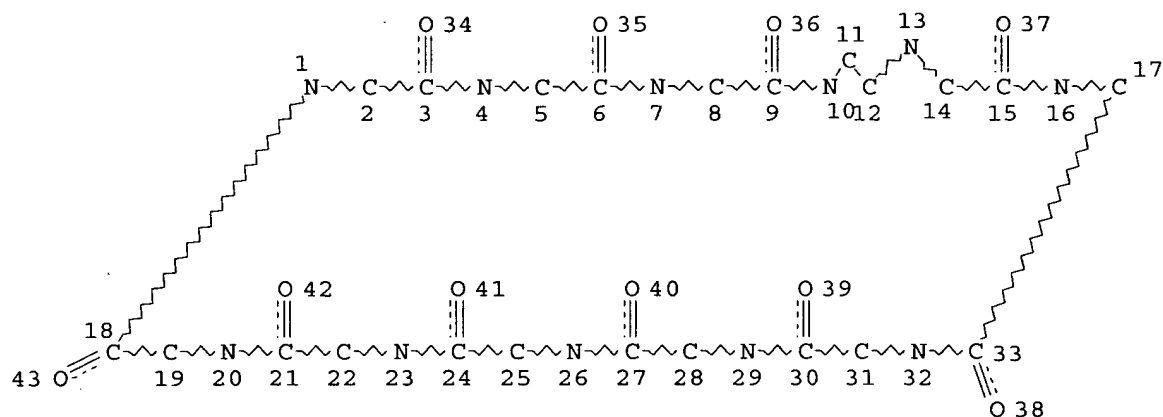
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The N2O4 Raman scattering cross section, 1.4 ± 10^{-31} cm², at a Raman shift of 1360 cm⁻¹ was measured by using a Q-switched ruby laser as the excitation source. The measured cross-section, 2.3 ± 10^{-30} cm², for N2 at a Raman shift of 2330 cm⁻¹ is compared with the value 8.3 ± 10^{-30} cm² reported by D. A. Leonard (1970). These cross sections can be used in determining concns. of the gases in air.

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L3 STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

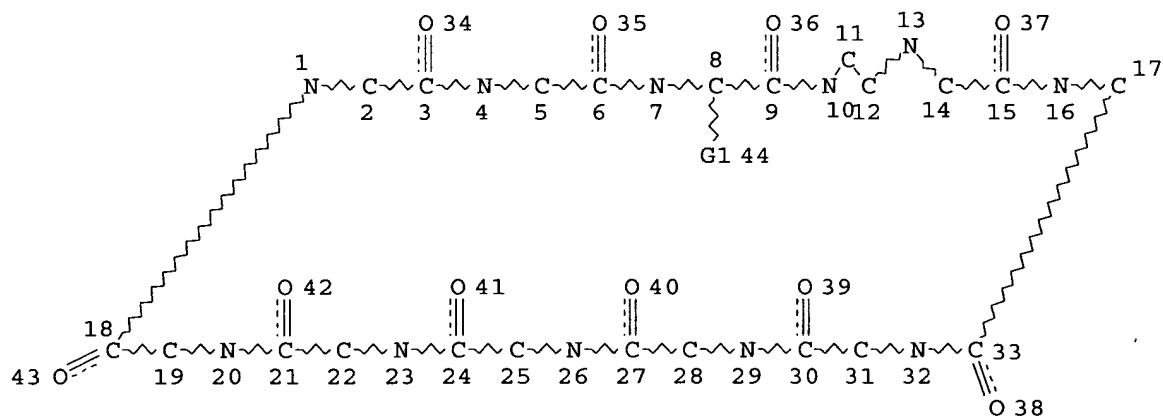
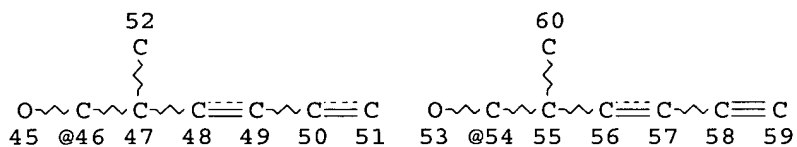
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NODE ATTRIBUTES:

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 60

STEREO ATTRIBUTES: NONE

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L17 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:652622 HCAPLUS

DOCUMENT NUMBER: 141:174478

TITLE: Preparation of **cyclosporins** for the treatment of immune disorders

INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Chen, Jason Shih-Hao

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 17 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004157768	A1	20040812	US 2003-360894	20030207
WO 2004072108	A1	20040826	WO 2004-US3582	20040206

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,

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 ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
 IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
 LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
 MZ, MZ, NA, NI
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
 BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
 MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
 GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN,
 GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2003-360894

A 20030207

OTHER SOURCE(S):

MARPAT 141:174478

AB The invention relates to **cyclosporin** analogs

cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is
 -NMeCH[CH(OR)CHMe-X-Y]CO- of stereo β R, γ R, where X is (CH₂)₂₋₈
 or CH₂CH:CH(CH₂)₂₋₅ and Y is D, halo, SCN, NCO, NCS, OH, OAc, halo,
 alkoxy, aryl, etc.; R is H or a protecting group; B is - α Abu-,
 -Val-, -Thr- or -Nva-; U is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-
 , -[O-acyl-D-Ser]- or -[O-(2-acyloxyethyl)-D-Ser]-] and their prodrugs or
 pharmaceutically-acceptable salts for the treatment of immune disorders.
 Thus, I [X = (CH₂)₂, Y = SPh, R = H, B = - α Abu-, and U is -D-Ala-]
 was prepared from **cyclosporin** A via acetylation, ozonolysis,
 borohydride reduction, mesylation, and reaction with thiophenol. Comps. of
 the invention showed IC₅₀ values 20 to 0.006 μ M in the calcineurin
 inhibition assay.

IT 83602-41-9P 121584-52-9P 699022-24-7P

699022-25-8P 733037-35-9P 733037-37-1P

733037-41-7P 733037-43-9P 733037-45-1P

733037-50-8P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of **cyclosporins** for treatment of immune disorders)

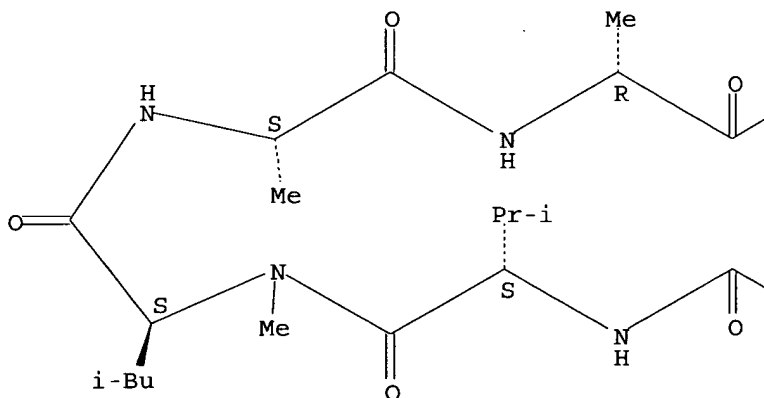
RN 83602-41-9 HCAPLUS

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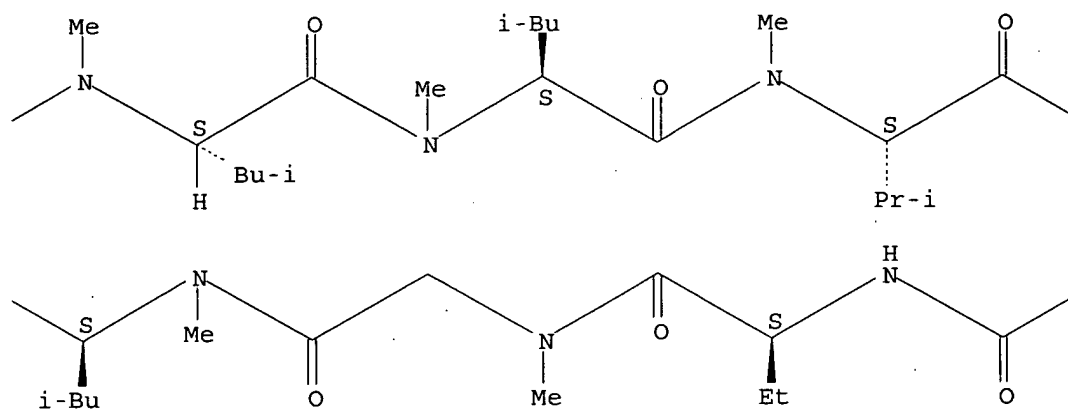
Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

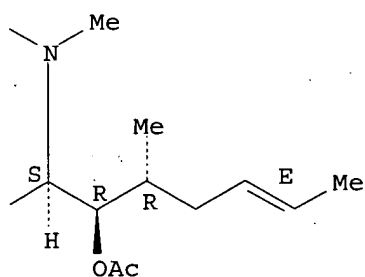
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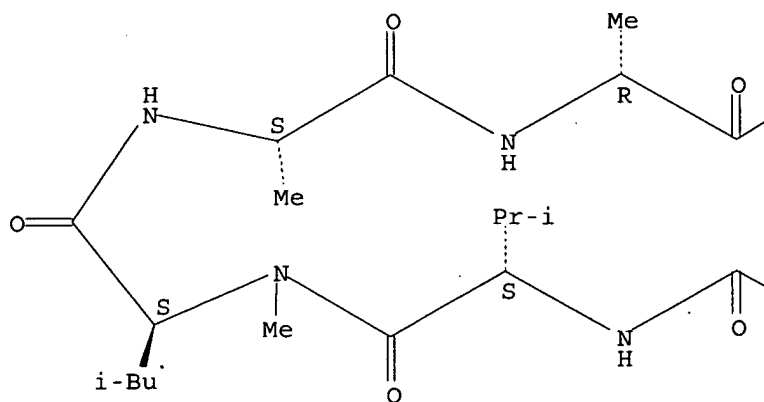


RN 121584-52-9 HCAPLUS

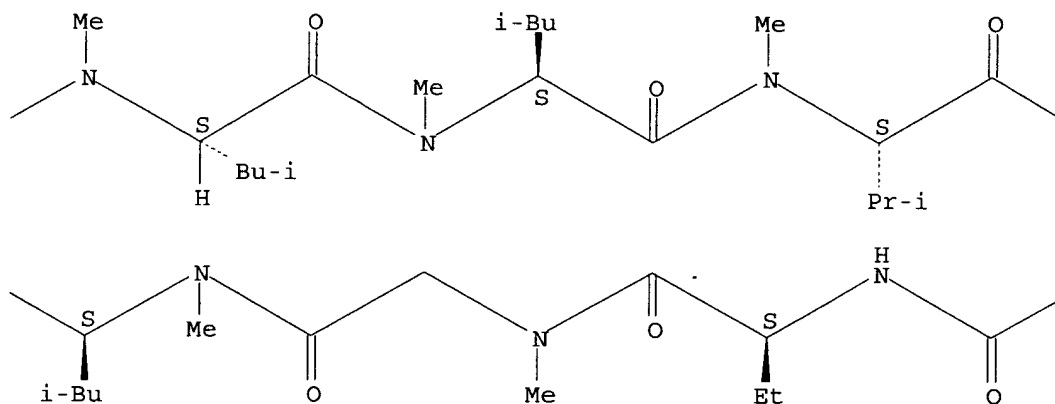
CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-N,4-dimethyl-6-oxo-L-norleucine]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

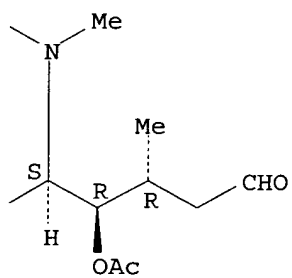
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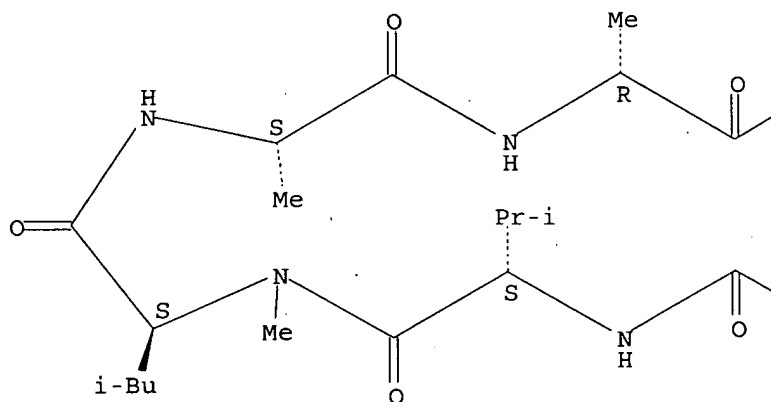


RN 699022-24-7 HCAPLUS

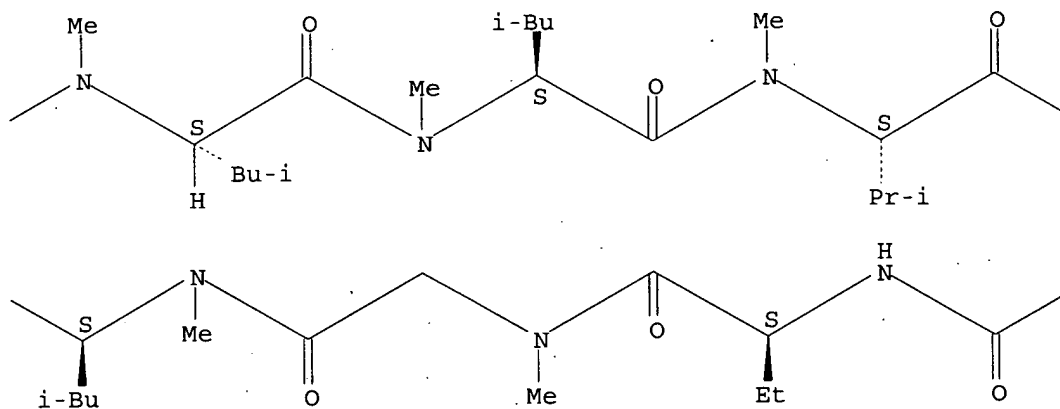
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

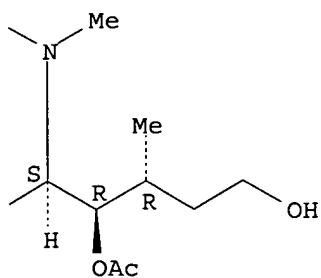
PAGE 1-A



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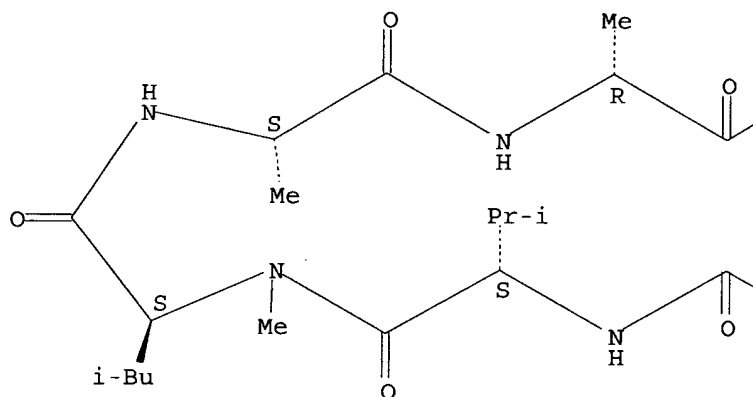


RN 699022-25-8 HCAPLUS

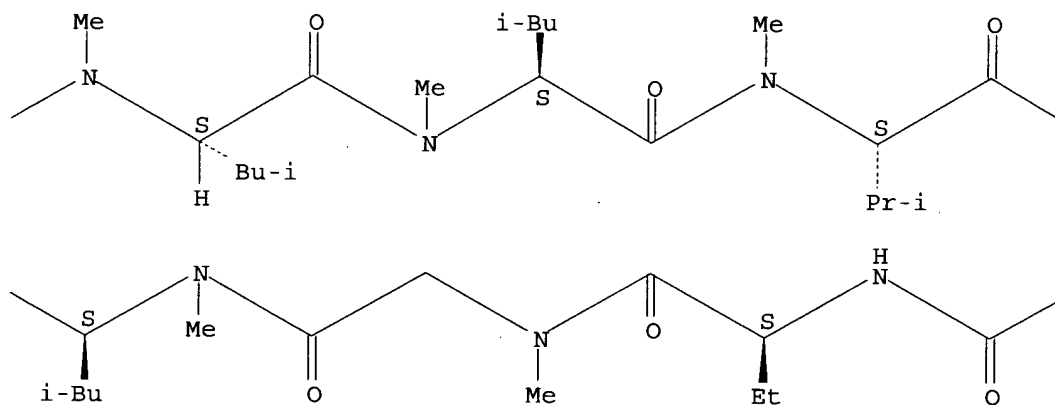
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-(methylsulfonyl)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

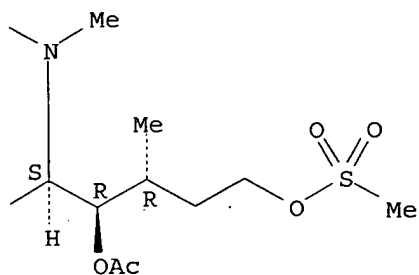
Absolute stereochemistry.

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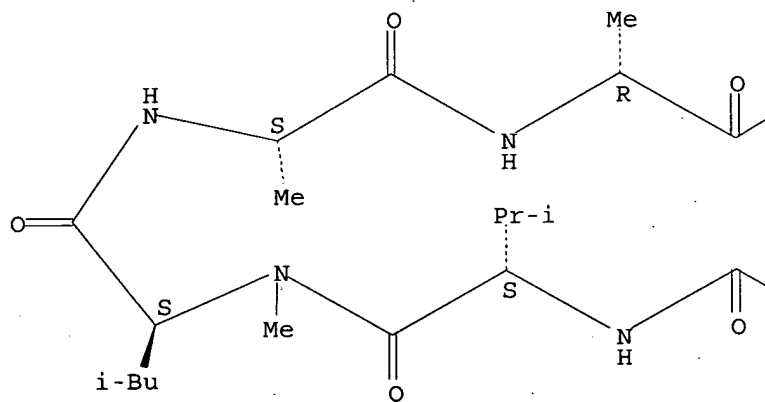




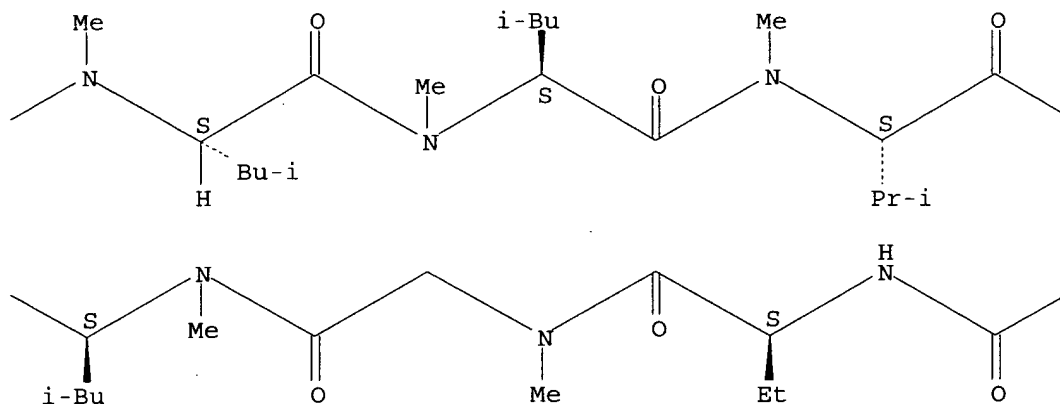
RN 733037-35-9 HCAPLUS

CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-S-phenyl-6-thio-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

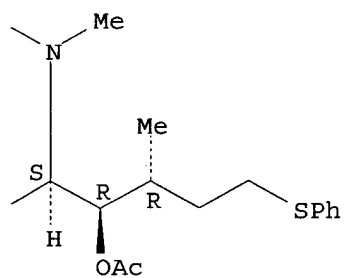
Absolute stereochemistry.



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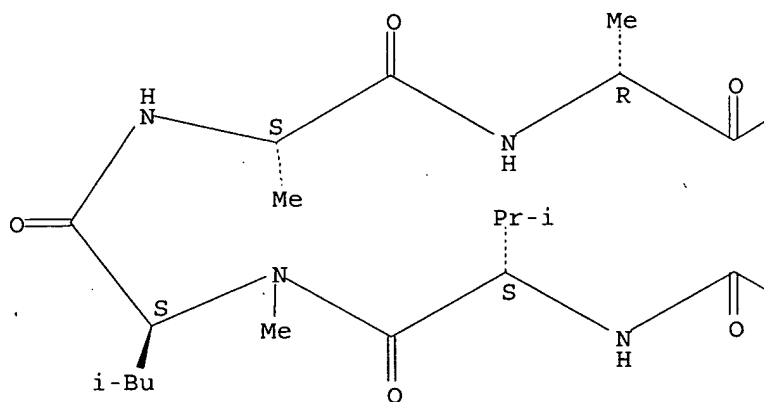


RN 733037-37-1 HCAPLUS

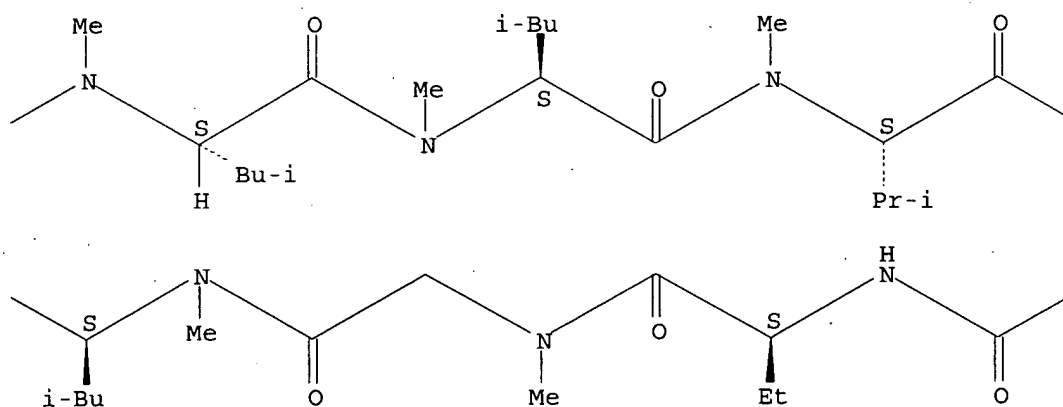
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-phenyl-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

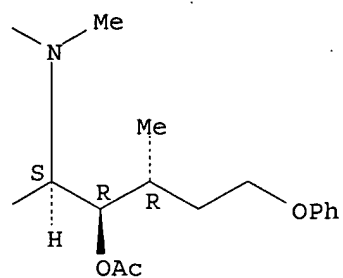
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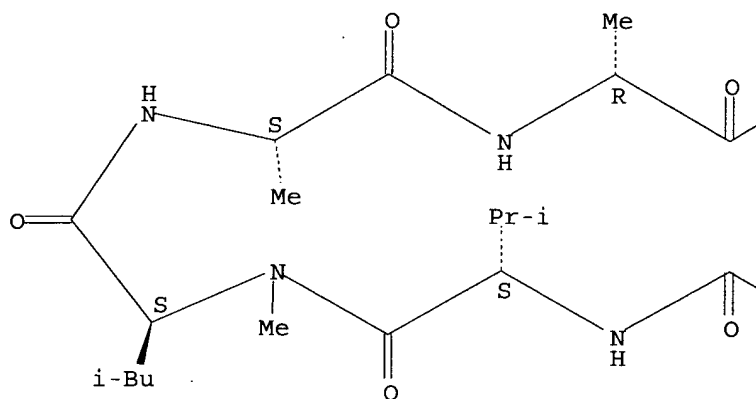


RN 733037-41-7 HCAPLUS

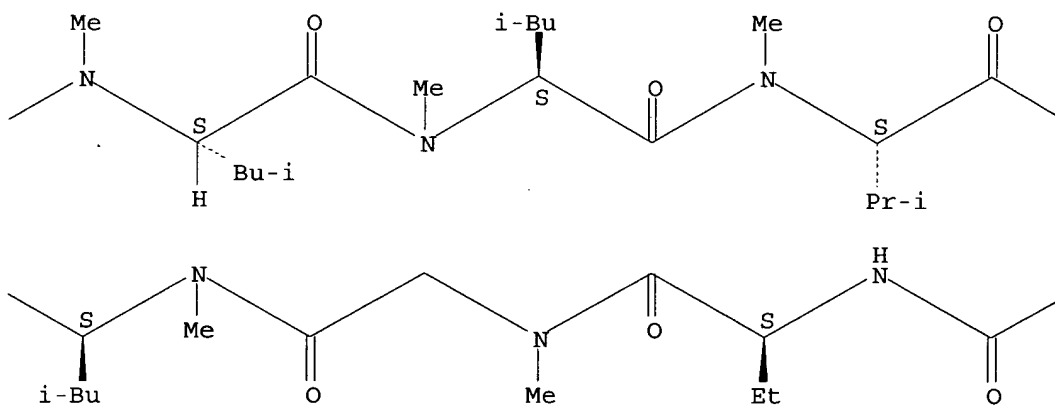
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-(phenylmethyl)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

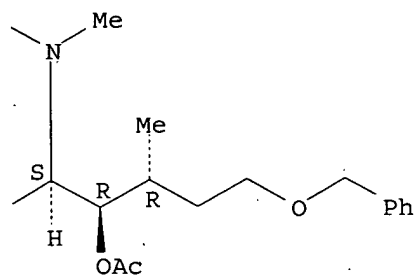
Absolute stereochemistry.

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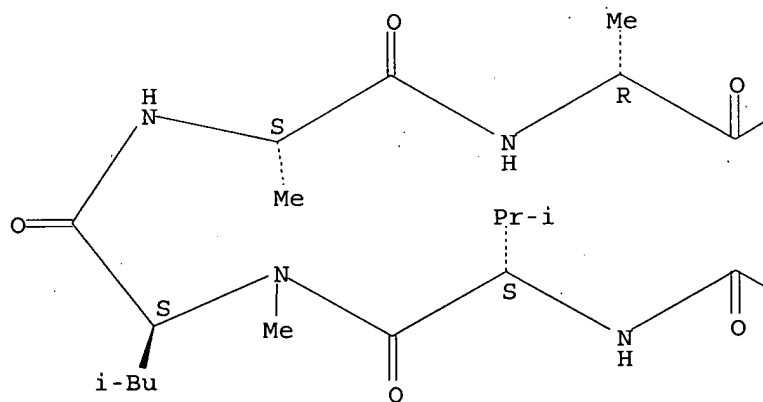




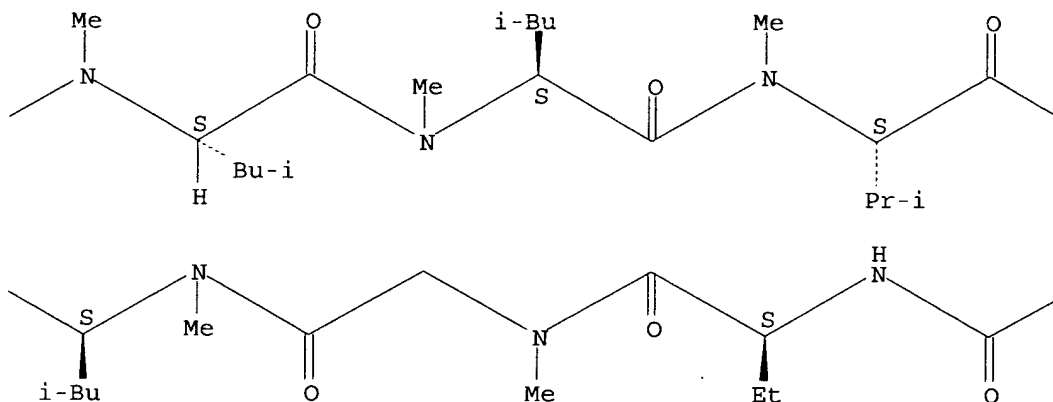
RN 733037-43-9 HCAPLUS

CN Cyclosporin A, 6-[3-O-acetyl-6-O-(2-chlorophenyl)-2,4,5-trideoxy-4-methyl-2-(methylamino)-D-arabino-hexonic acid] - (9CI) (CA INDEX NAME)

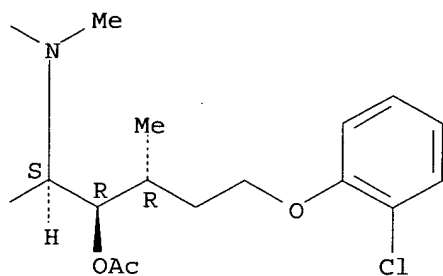
Absolute stereochemistry.



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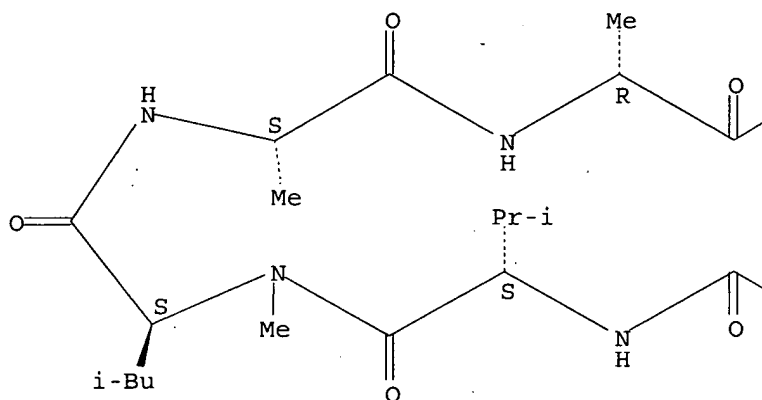


RN 733037-45-1 HCAPLUS

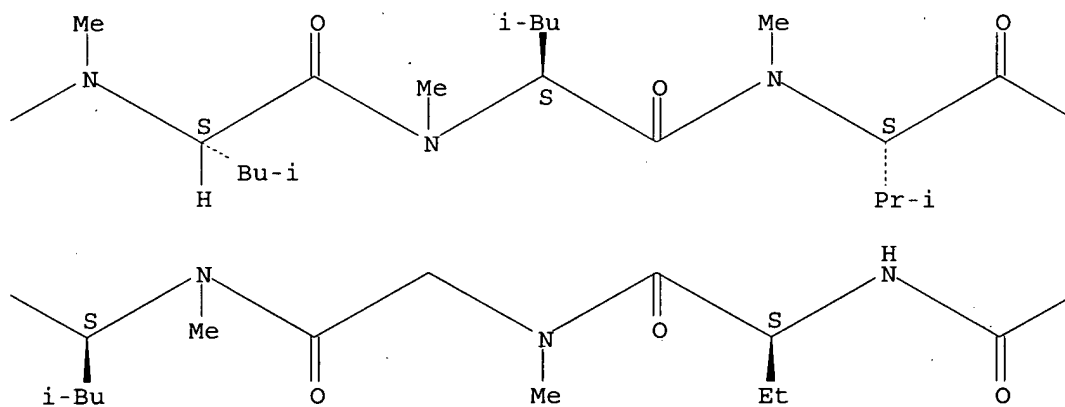
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-2-pyridinyl-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

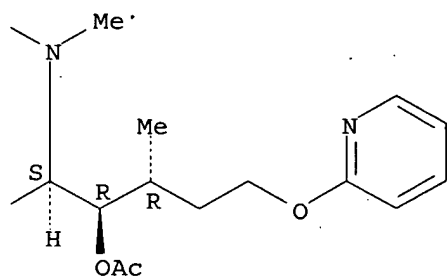
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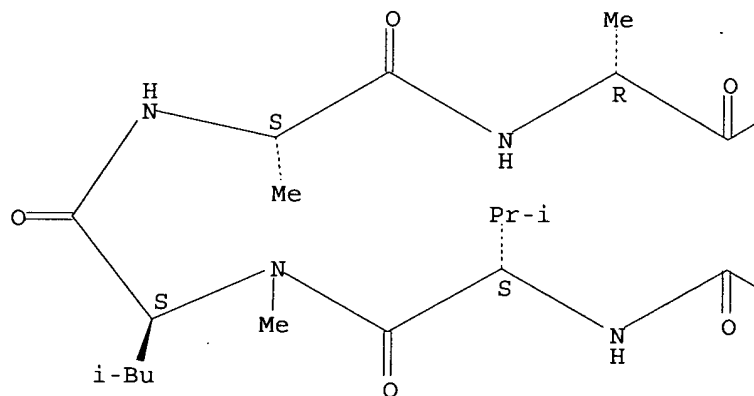


RN , 733037-50-8 HCAPLUS

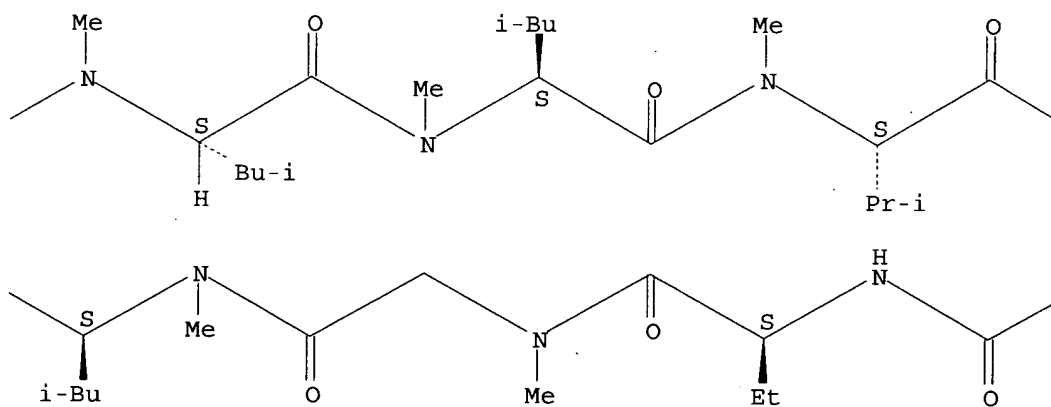
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3,9-bis(acetyloxy)-4-methyl-2-(methylamino)-6-nonenoic acid]- (9CI) (CA INDEX NAME)

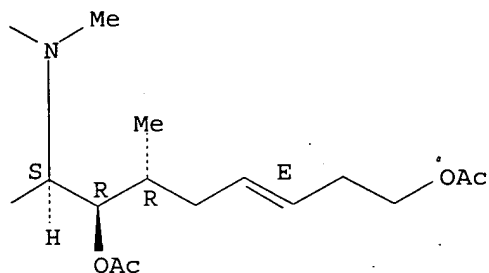
Absolute stereochemistry.
Double bond geometry as shown.

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IT 733037-36-0P 733037-38-2P 733037-39-3P
 733037-40-6P 733037-42-8P 733037-44-0P
 733037-46-2P 733037-47-3P 733037-48-4P
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 733037-53-1P

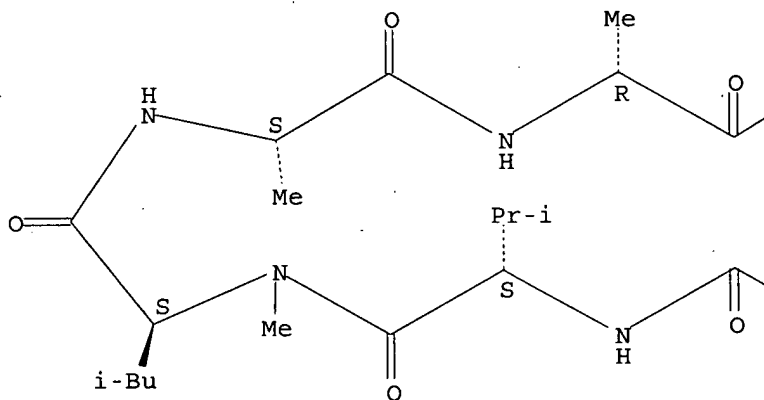
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of **cyclosporins** for treatment of immune disorders)

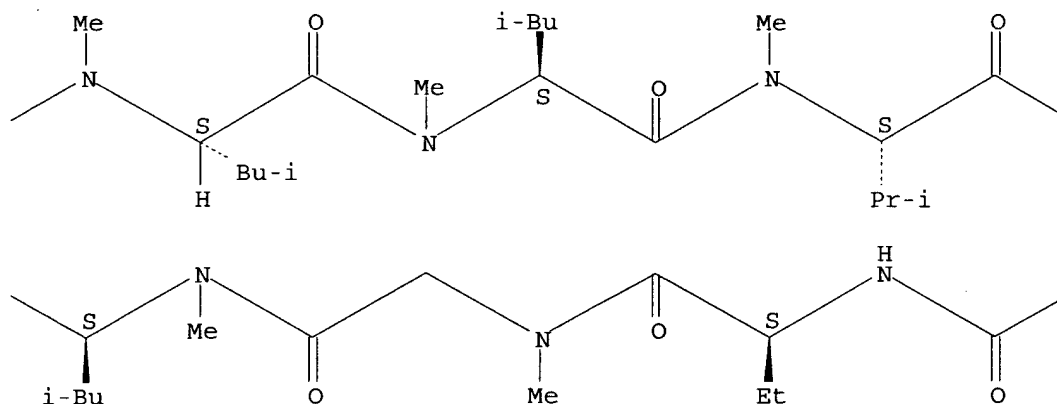
RN 733037-36-0 HCAPLUS

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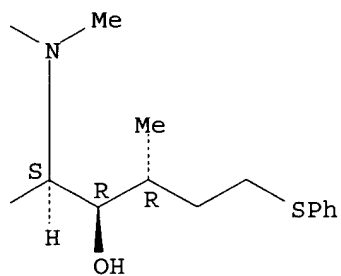
Absolute stereochemistry.



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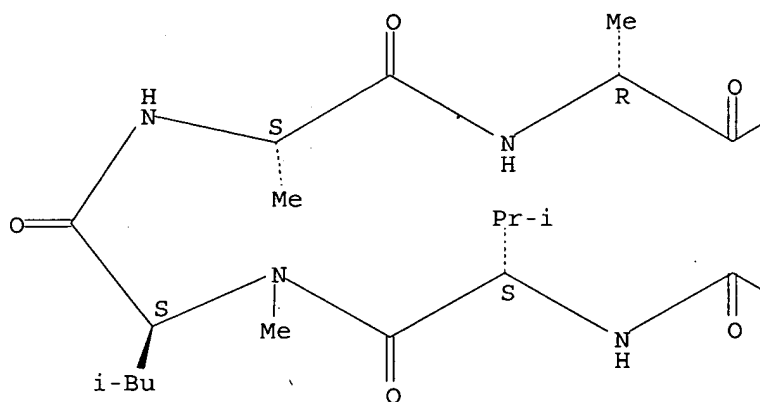


RN 733037-38-2 HCAPLUS

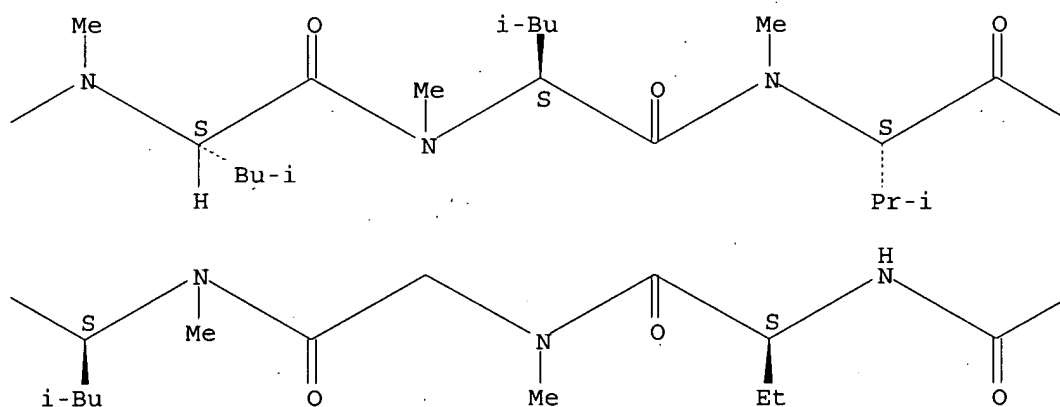
CN Cyclosporin A, 6-[2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-phenyl-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

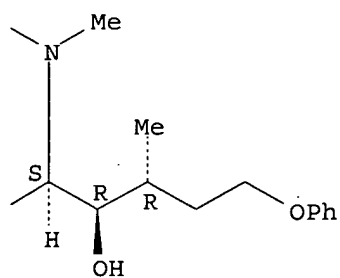
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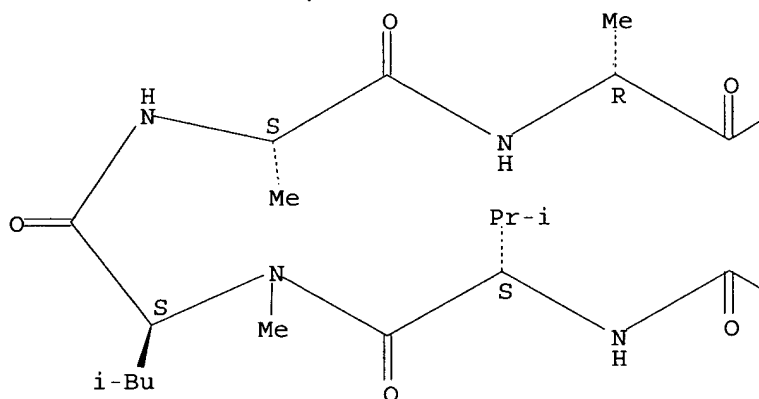


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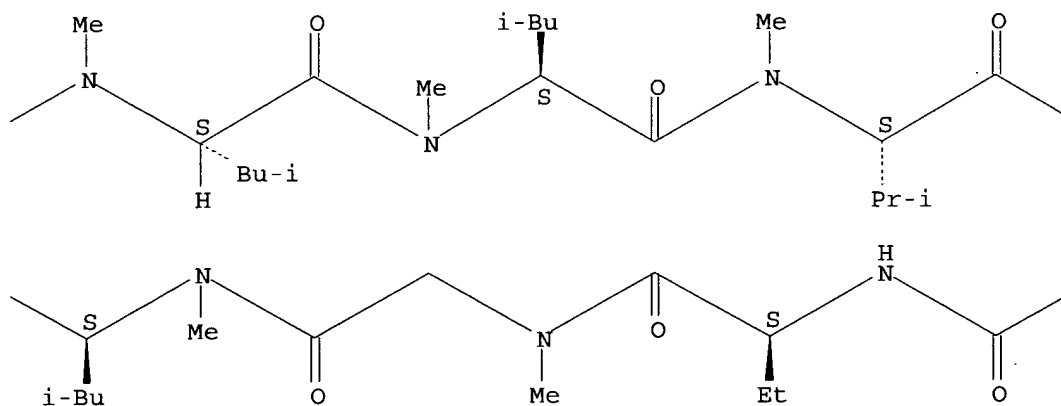
CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-6-S-ethyl-4-methyl-2-(methylamino)-6-thio-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

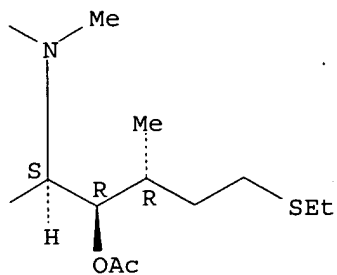
Absolute stereochemistry.

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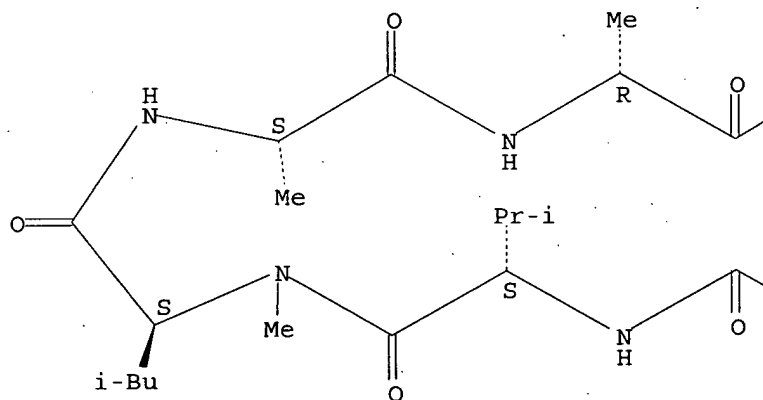




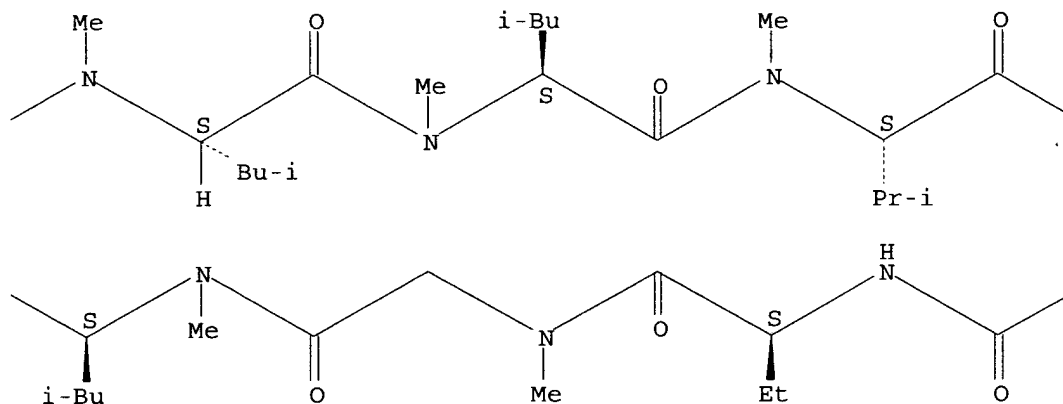
RN 733037-40-6 HCAPLUS

CN Cyclosporin A, 6-[2,4,5-trideoxy-6-S-ethyl-4-methyl-2-(methylamino)-6-thio-D-arabino-hexonic acid] - (9CI) (CA INDEX NAME)

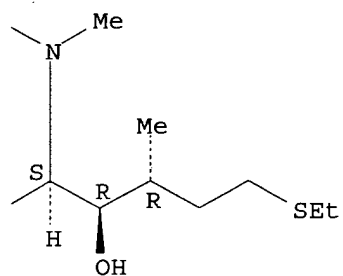
Absolute stereochemistry.



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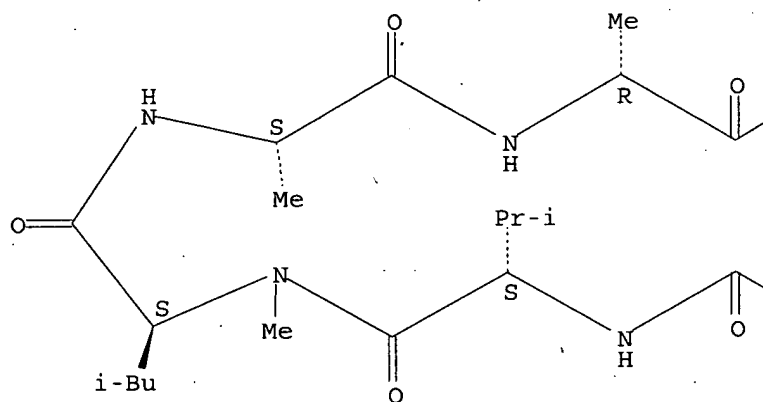


RN 733037-42-8 HCAPLUS

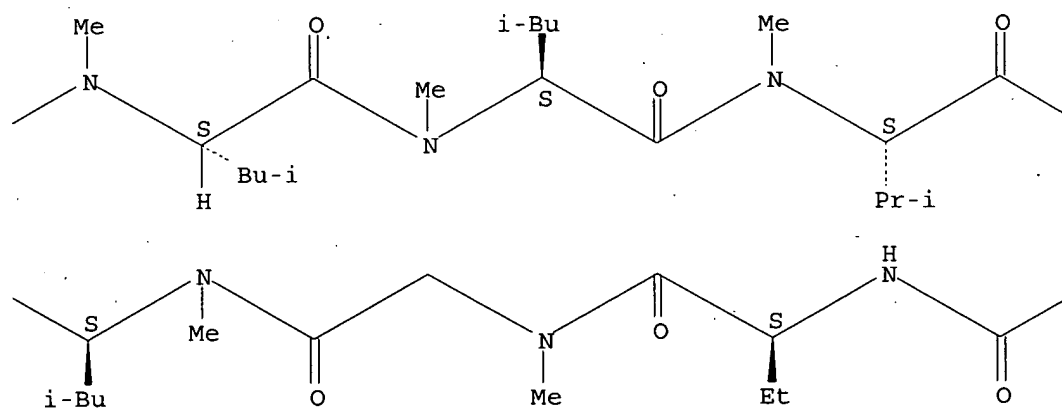
CN Cyclosporin A, 6-[2,4,5-trideoxy-4-methyl-2-(methylamino)-6-O-(phenylmethyl)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

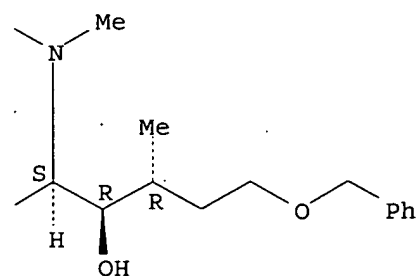
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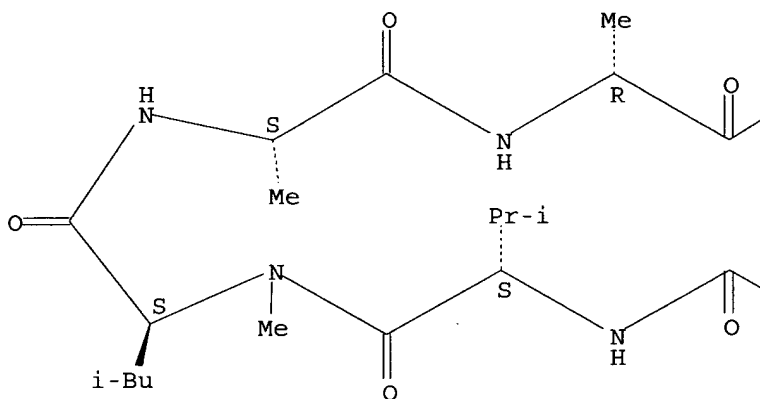


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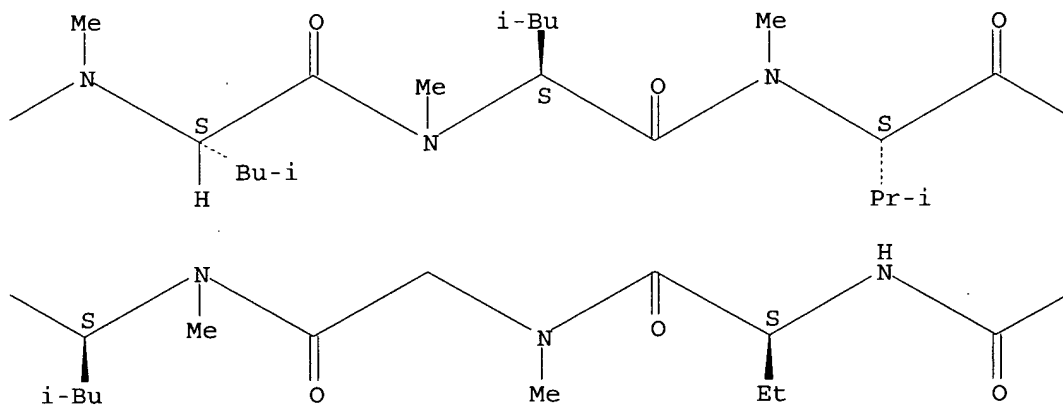
CN Cyclosporin A, 6-[6-O-(2-chlorophenyl)-2,4,5-trideoxy-4-methyl-2-(methylamino)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

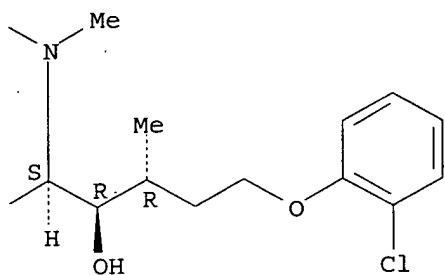
Absolute stereochemistry.

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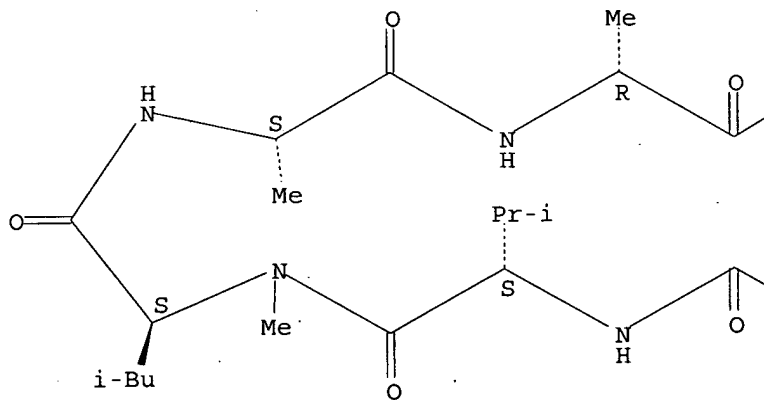




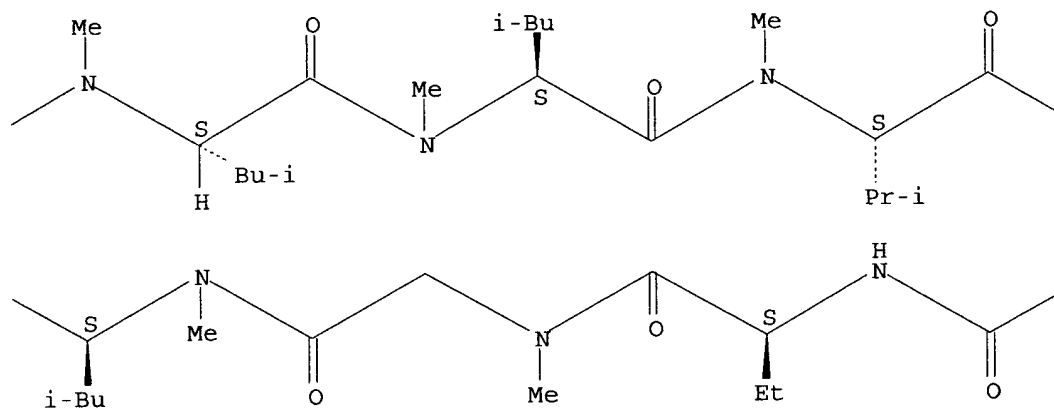
RN 733037-46-2 HCAPLUS

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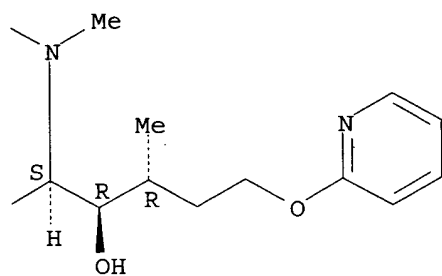
Absolute stereochemistry.



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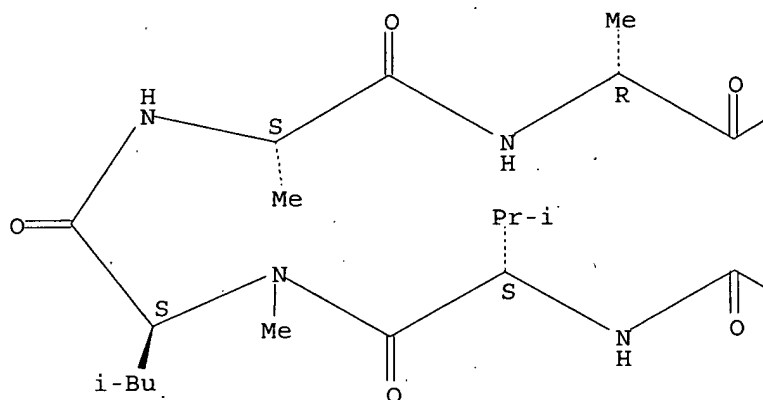
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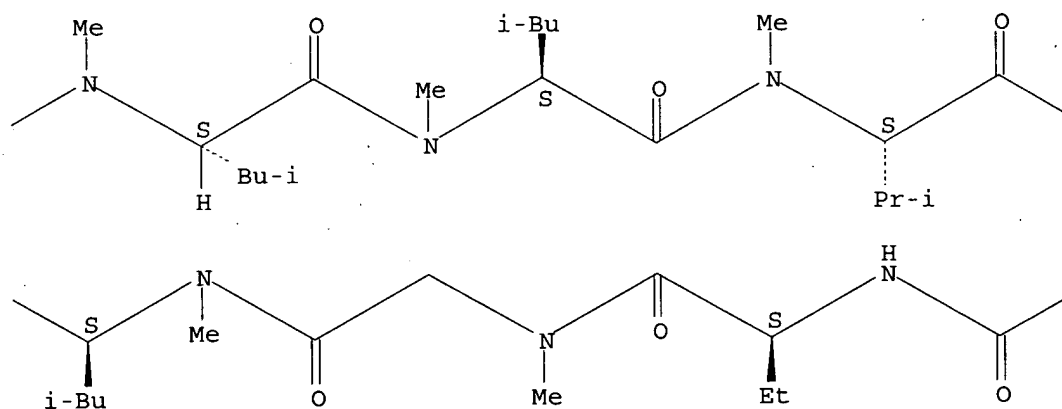
RN 733037-47-3 HCAPLUS
 CN Cyclosporin A, 6-[3-O-acetyl-2,4,5-trideoxy-4-methyl-2-(methylamino)-6-S-(2-methylphenyl)-6-thio-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

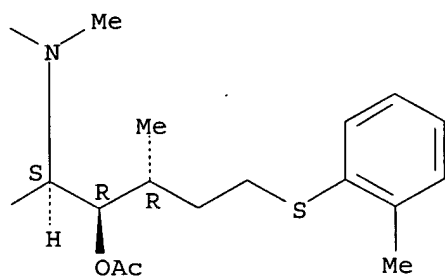
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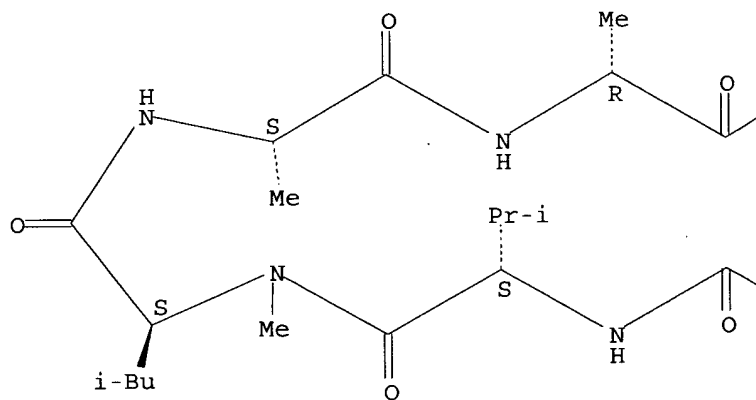


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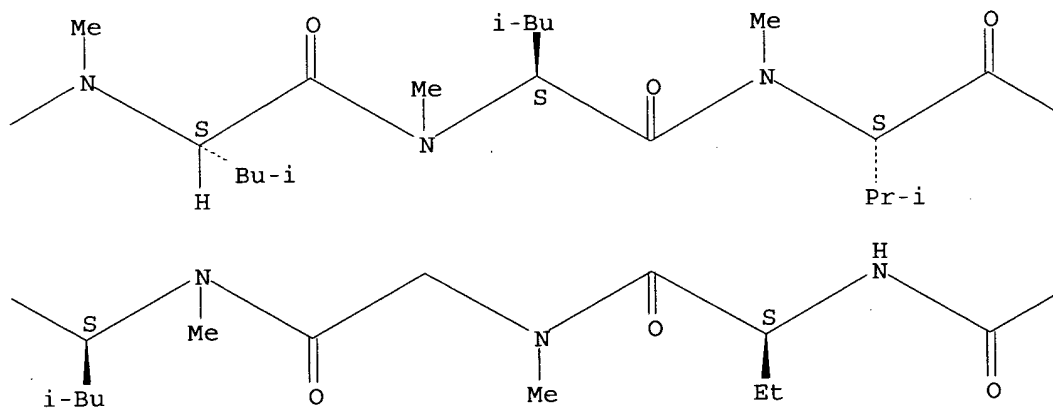
CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-N,4-dimethyl-6-thiocyanato-L-norleucine]- (9CI) (CA INDEX NAME)

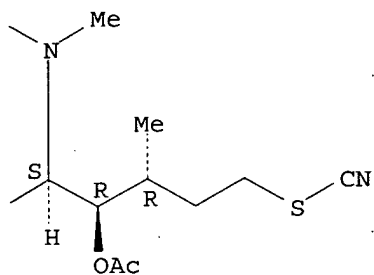
Absolute stereochemistry.

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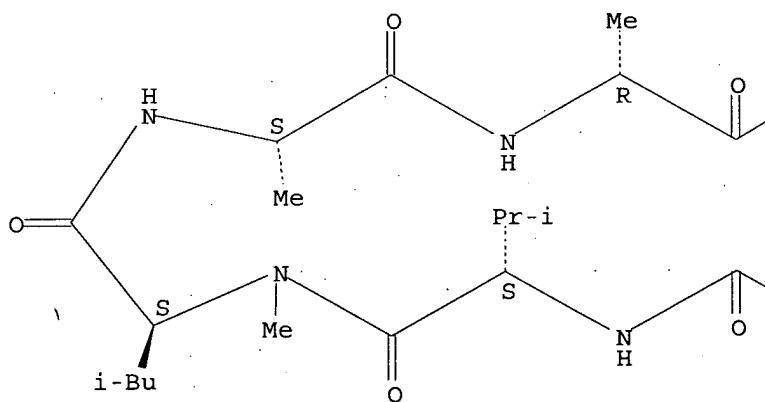




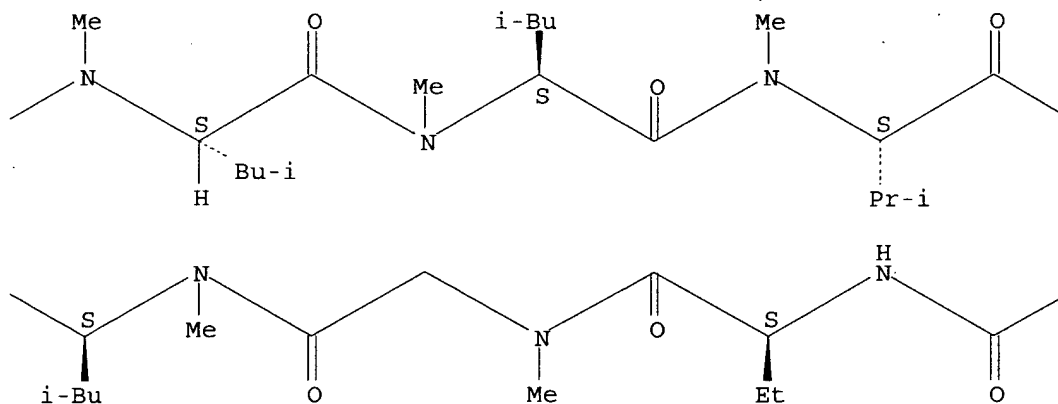
RN 733037-49-5 HCAPLUS

CN Cyclosporin A, 6-[3-O-acetyl-2,4,5,6-tetradecoxy-6-isocyanato-4-methyl-2-(methylamino)-D-arabino-hexonic acid]- (9CI) (CA INDEX NAME)

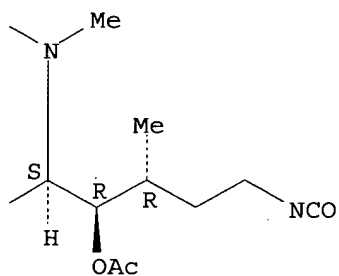
Absolute stereochemistry.



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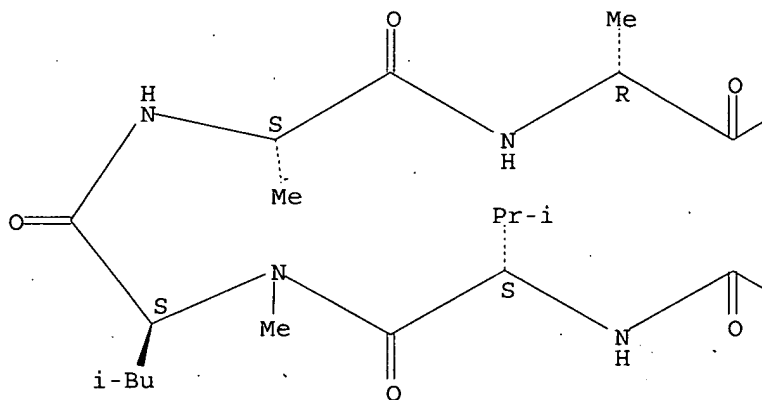


RN 733037-51-9 HCAPLUS

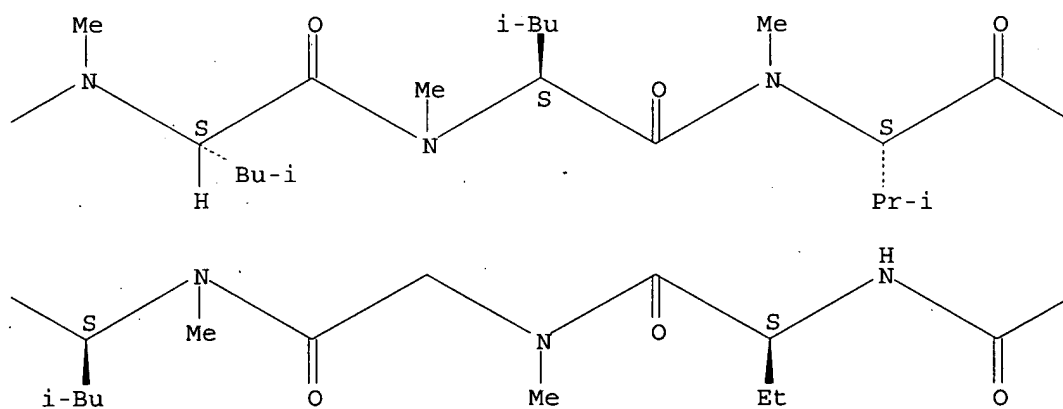
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-9-(acetyloxy)-3-hydroxy-4-methyl-2-(methylamino)-6-nonenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

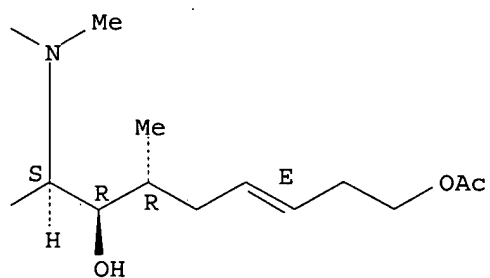
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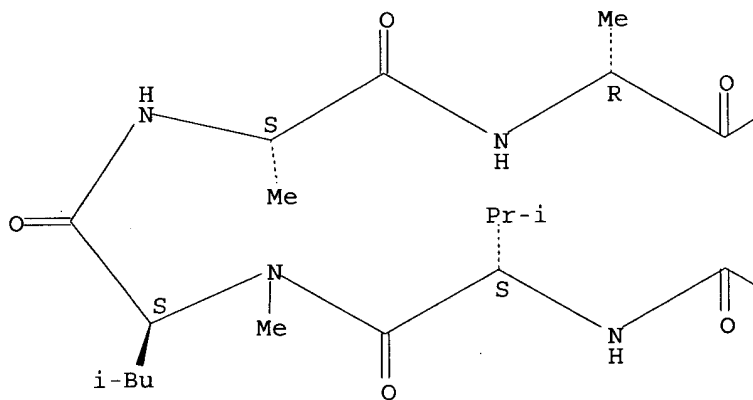


RN 733037-52-0 HCAPLUS

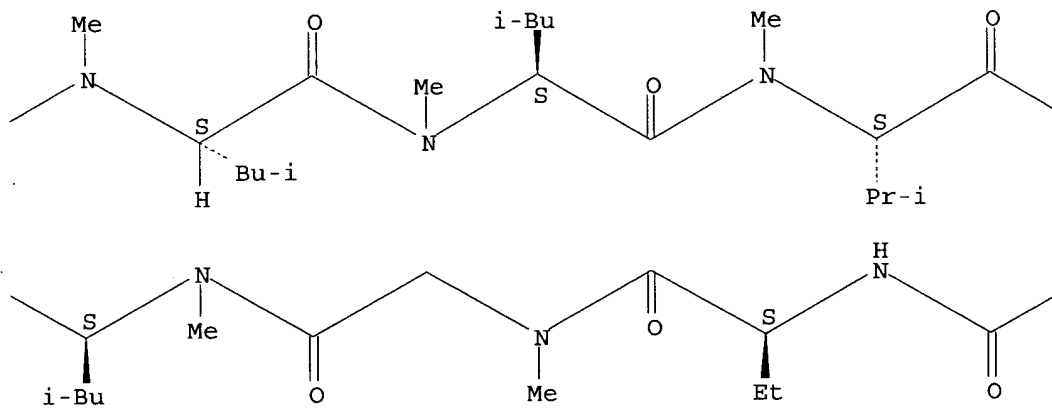
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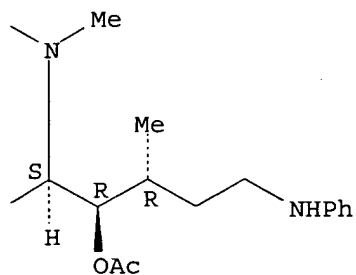
Absolute stereochemistry.

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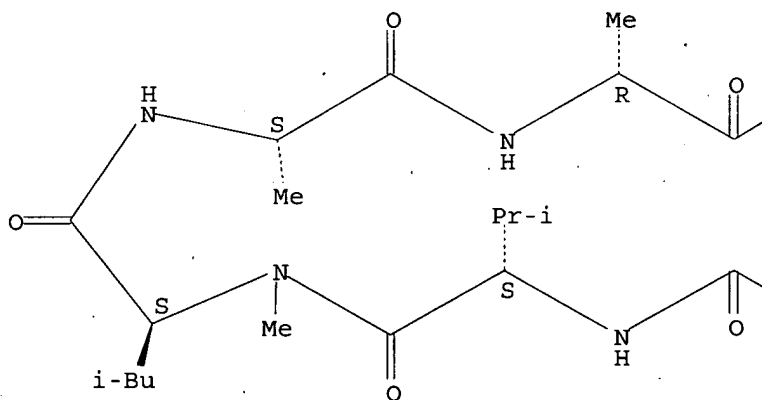




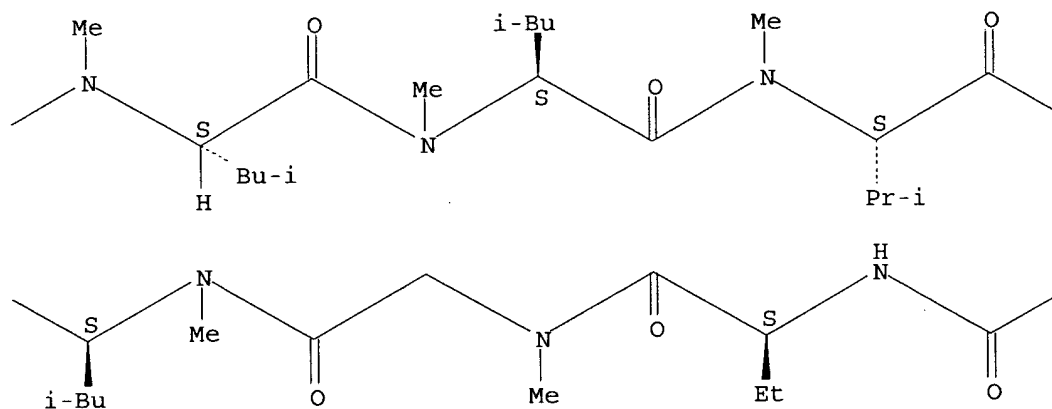
RN 733037-53-1 HCAPLUS

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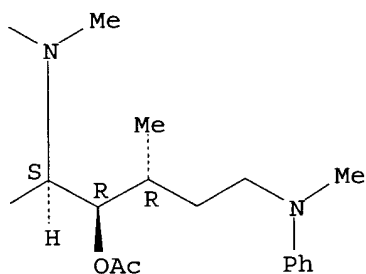
Absolute stereochemistry.



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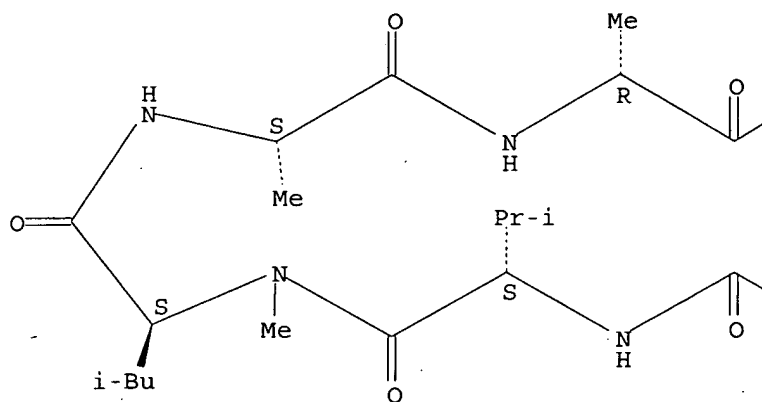
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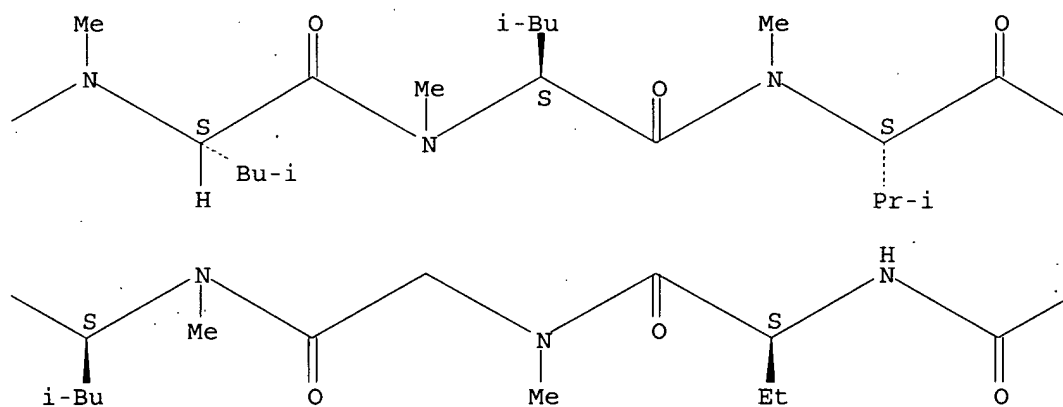
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 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of cyclosporins for treatment of immune disorders)
 RN 59865-13-3 HCAPLUS
 CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

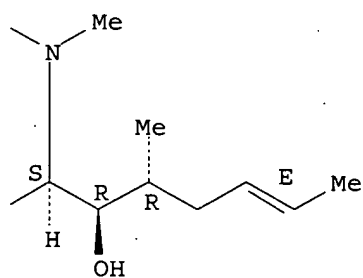
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L17 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:473331 HCAPLUS
 DOCUMENT NUMBER: 141:23910
 TITLE: Preparation of **cyclosporins** for the treatment of immune disorders
 INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Chen, Jason Shih-Hao
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 15 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004110666	A1	20040610	US 2002-309934	20021204
WO 2004050687	A2	20040617	WO 2003-US38627	20031204
WO 2004050687	A3	20040805		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-309934 A 20021204

OTHER SOURCE(S): MARPAT 141:23910

AB The invention relates to **cyclosporin** analogs
 cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is -NMeCH[CH(OR)CHMe-X-Y]CO- of stereo α S, β R, where X is (CH₂)₁₋₈ or CH₂CH:CH(CH₂)₂₋₅ and Y is OH, OAc, halo, N₃, CN, OSO₂R₁₀ (R₁₀ is F, Me, CF₃, Ph, MePh); or X-Y is CH:CH₂, CHO, or Et; R is H or a protecting group; B is - α Abu-, -Val-, -Thr- or -Nva-; U is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-, -[O-acyl-D-Ser]- or -[O-(2-acyloxyethyl)-D-Ser]-] and their prodrugs or pharmaceutically-acceptable salts for the treatment of immune disorders. Thus, I [X = (CH₂)₂, Y = N₃, R = H, B = - α Abu-, and U is -D-Ala-] was prepared from **cyclosporin** A via ozonolysis and azidation reactions. Compds. of the invention showed IC₅₀ values 20 to 0.006 μ M in the calcineurin inhibition assay.

IT 83602-41-9P 121584-52-9P 699022-24-7P
 699022-25-8P 699022-26-9P 699022-28-1P
 699022-30-5P 699022-32-7P 699022-35-0P
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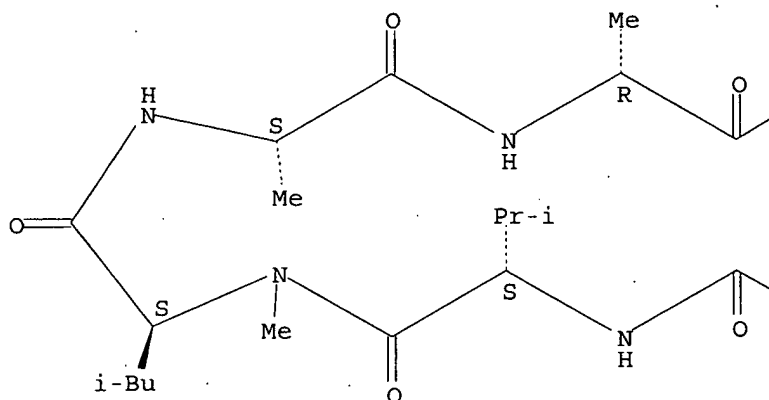
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (preparation of **cyclosporins** for treatment of immune disorders)

RN 83602-41-9 HCAPLUS

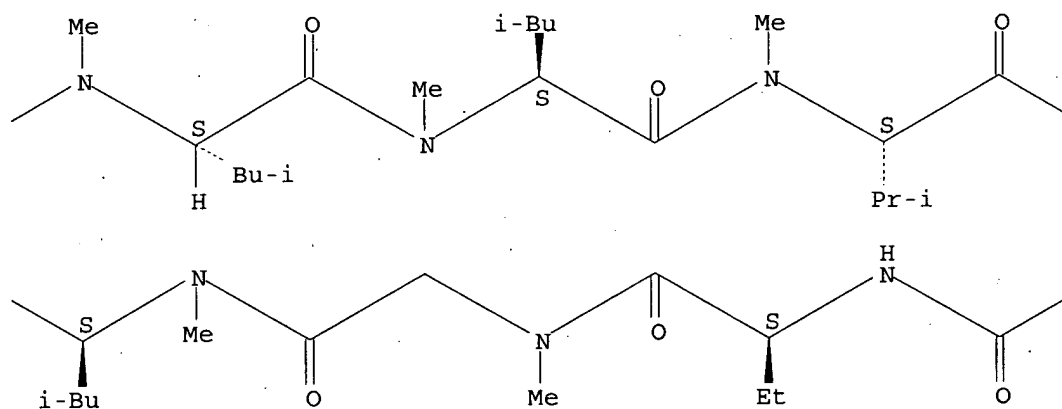
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Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

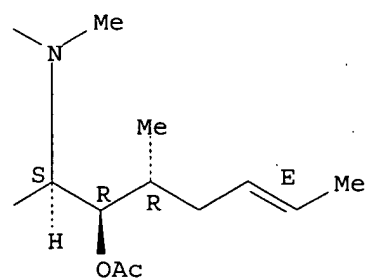
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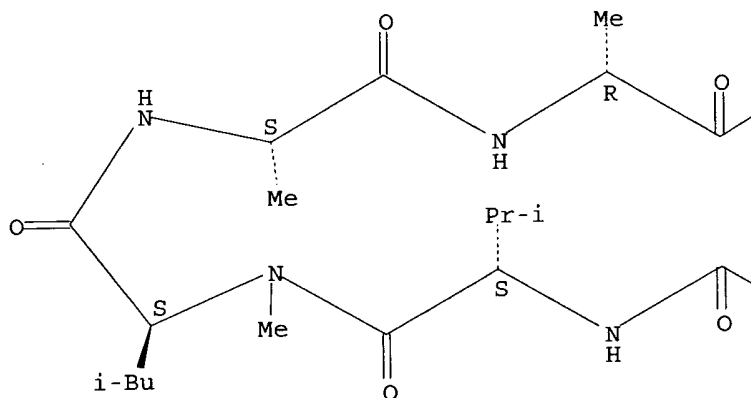
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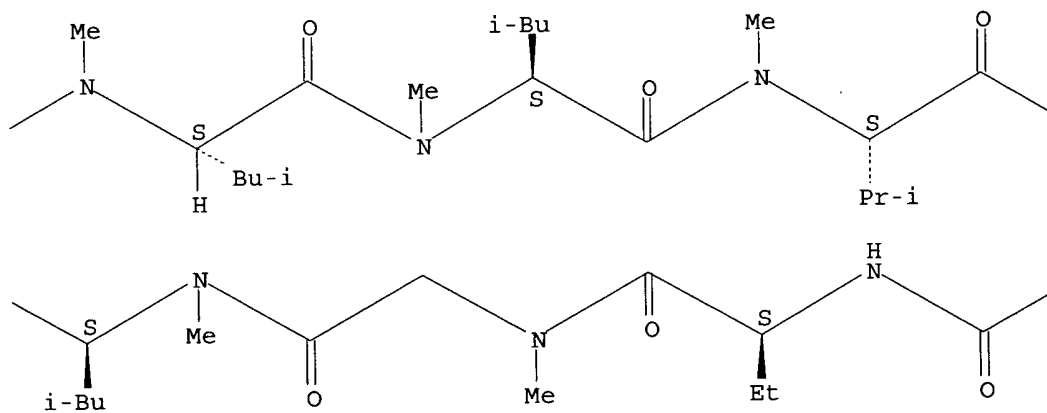
(9CI) (CA INDEX NAME)

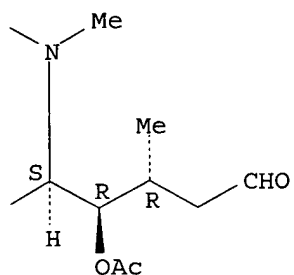
Absolute stereochemistry. Rotation (-).

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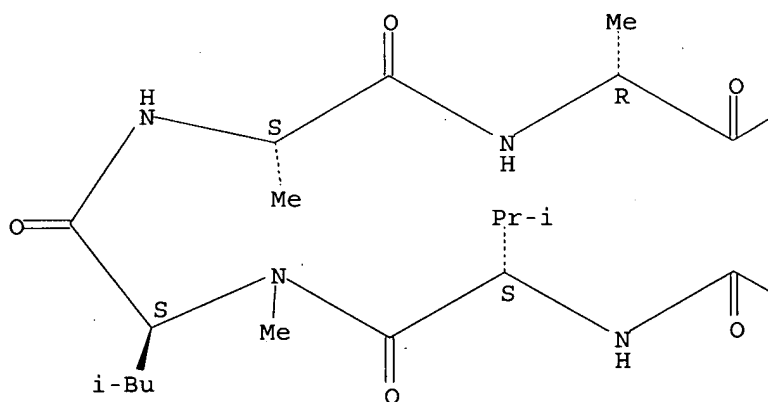




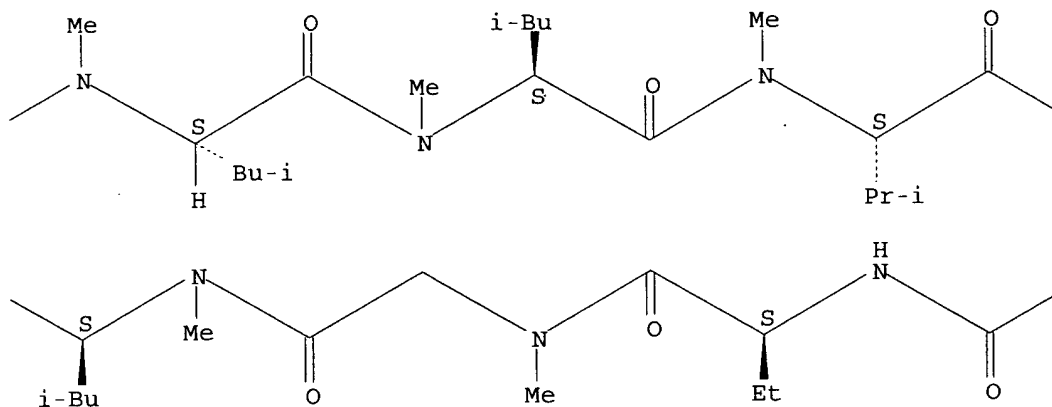
RN 699022-24-7 HCAPLUS

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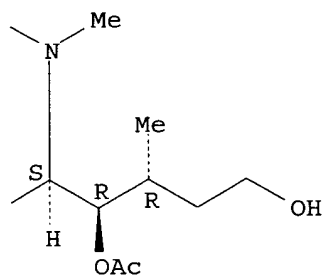
Absolute stereochemistry.



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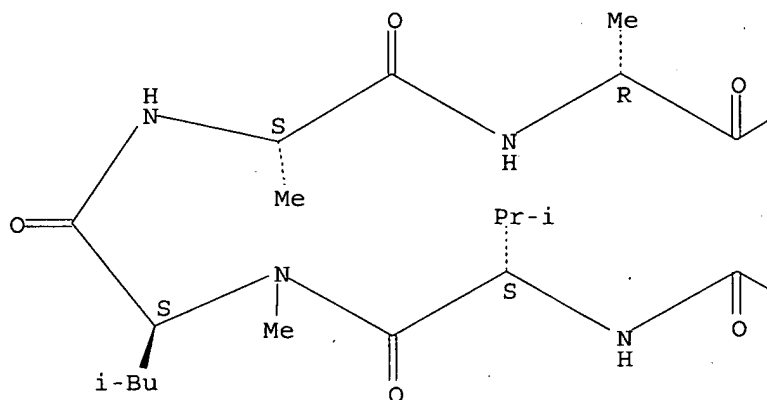


RN 699022-25-8 HCAPLUS

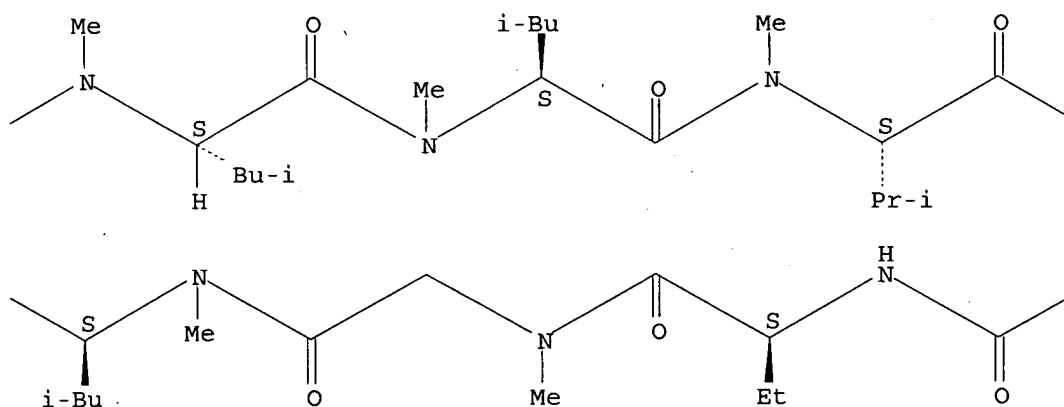
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Absolute stereochemistry.

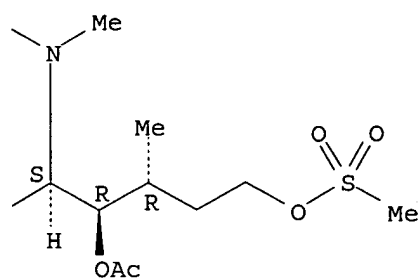
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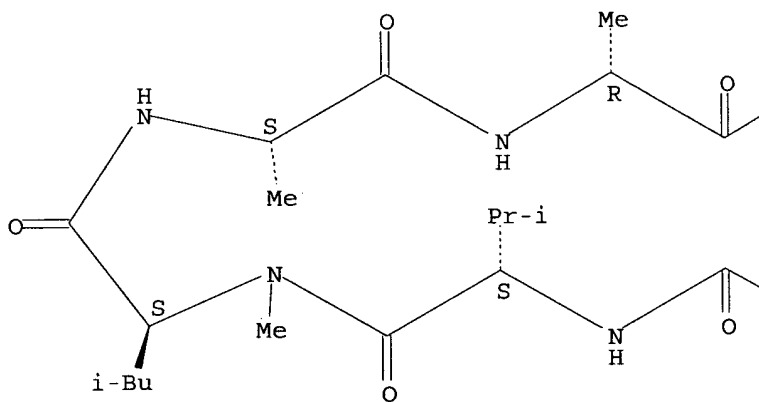


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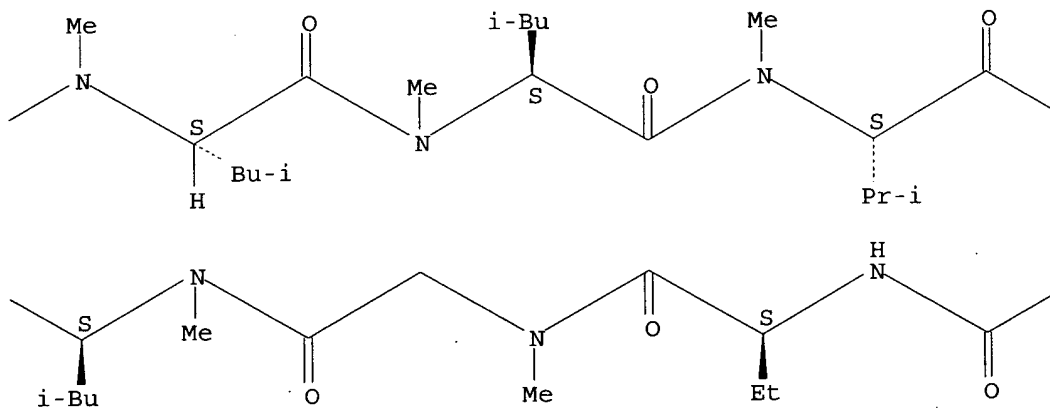
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(9CI) (CA INDEX NAME)

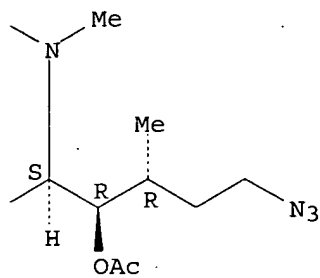
Absolute stereochemistry.

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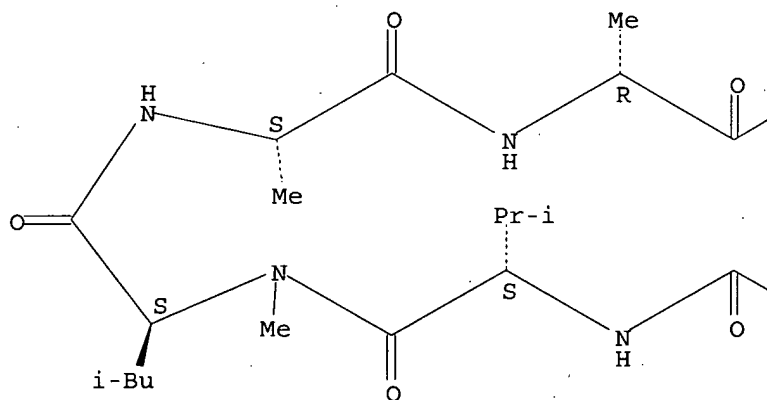




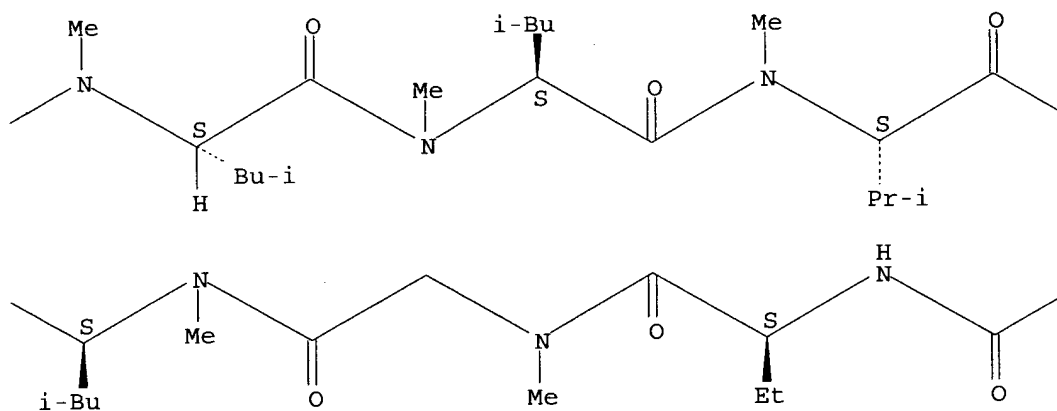
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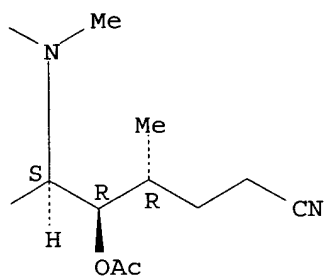
Absolute stereochemistry.



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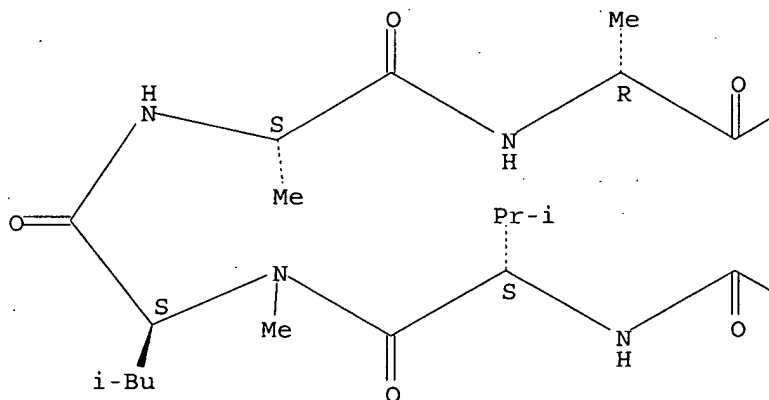
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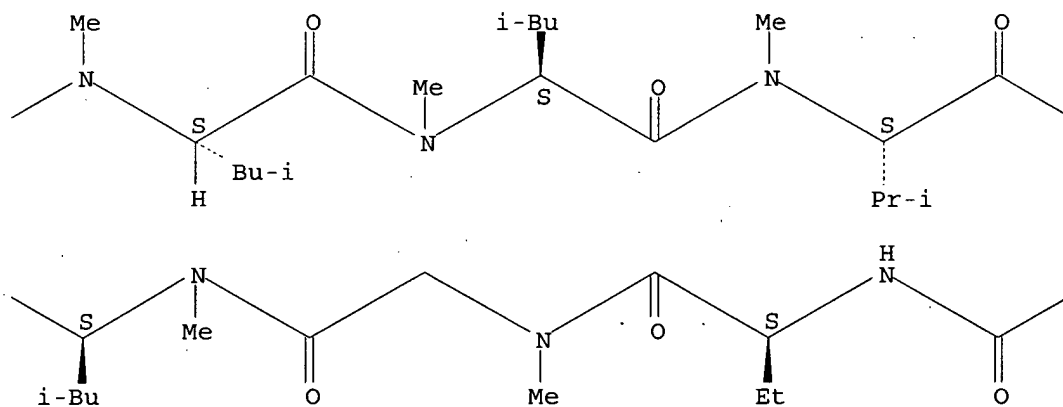
RN 699022-30-5 HCAPLUS
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Absolute stereochemistry.

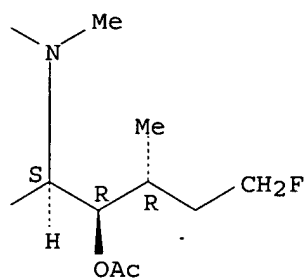
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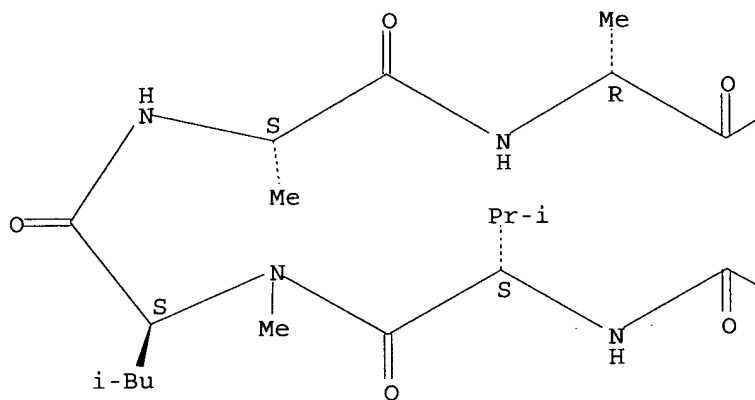


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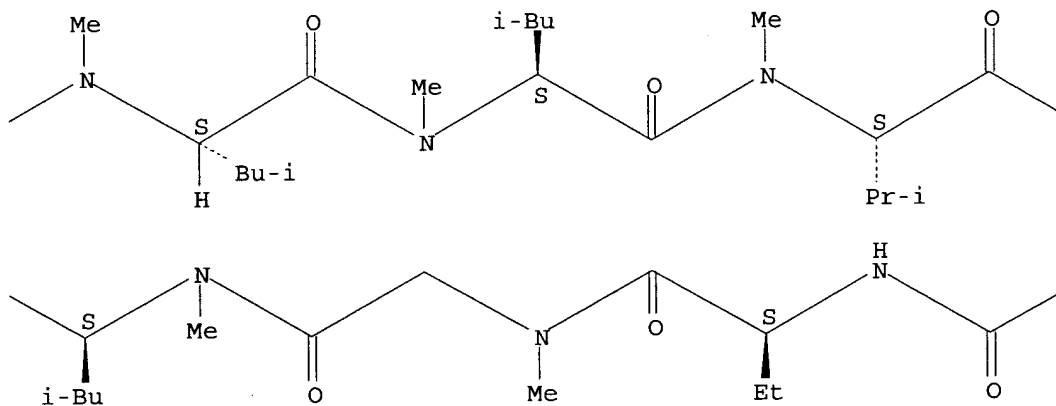
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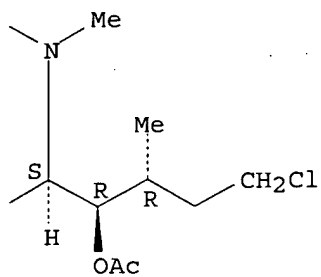
Absolute stereochemistry.

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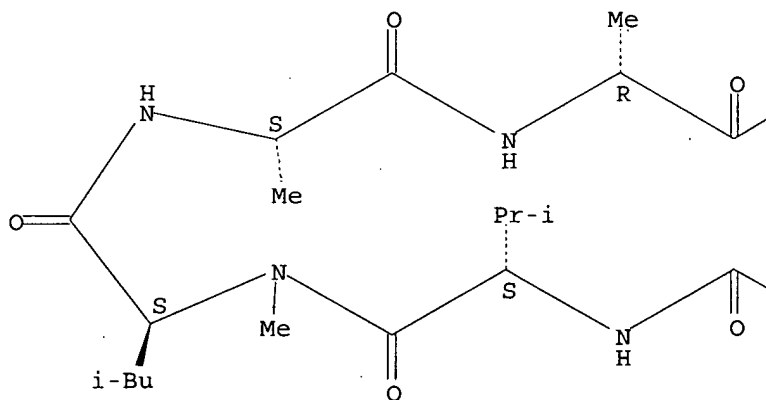




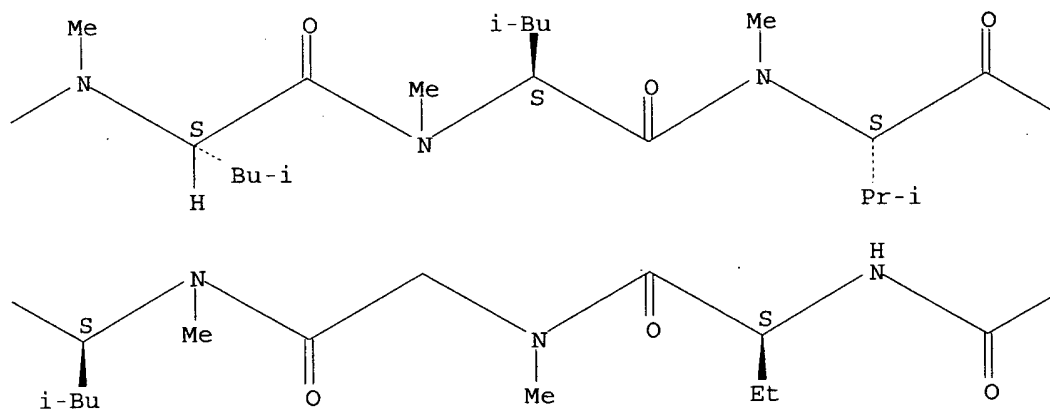
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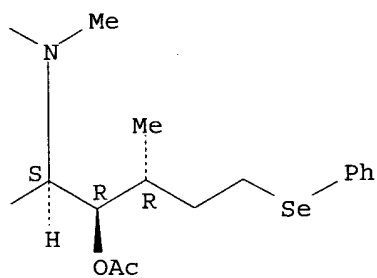
Absolute stereochemistry.



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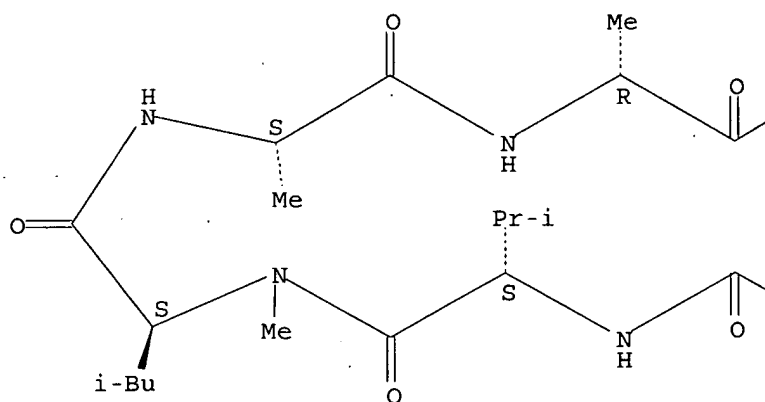


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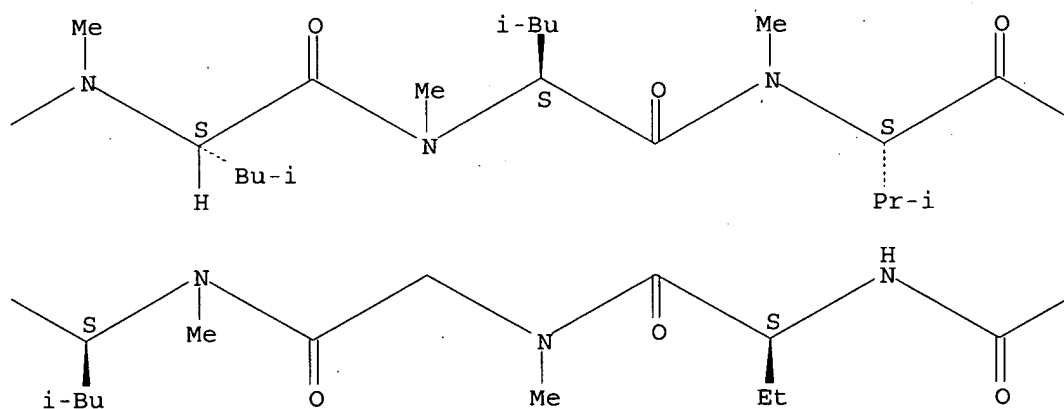
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Absolute stereochemistry.

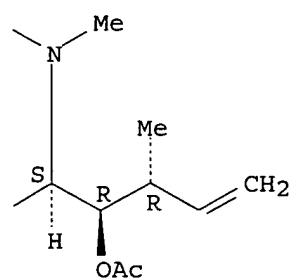
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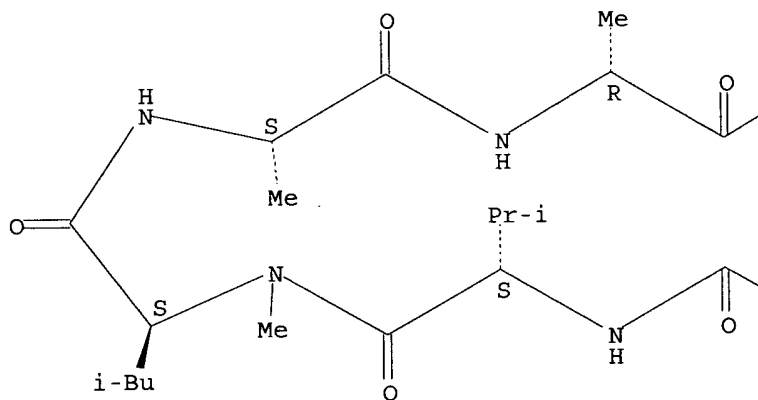


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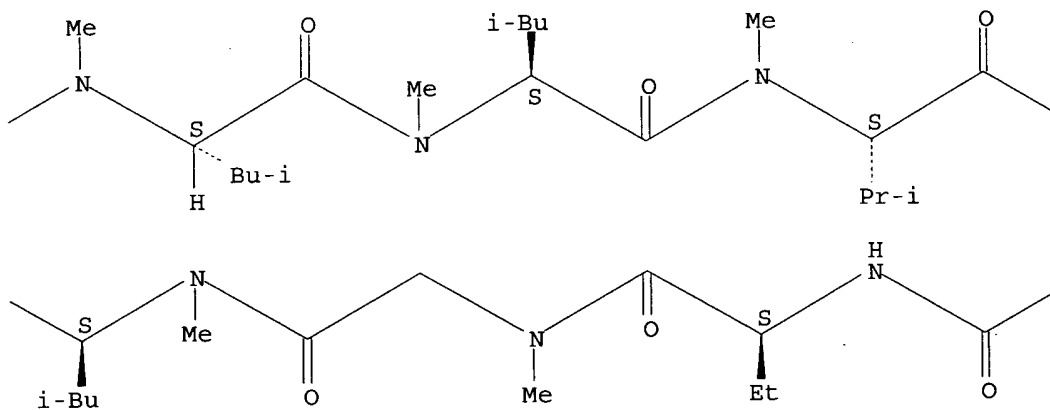
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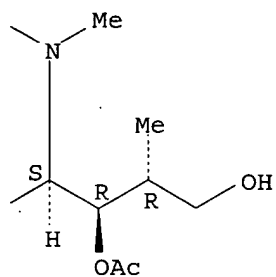
Absolute stereochemistry.

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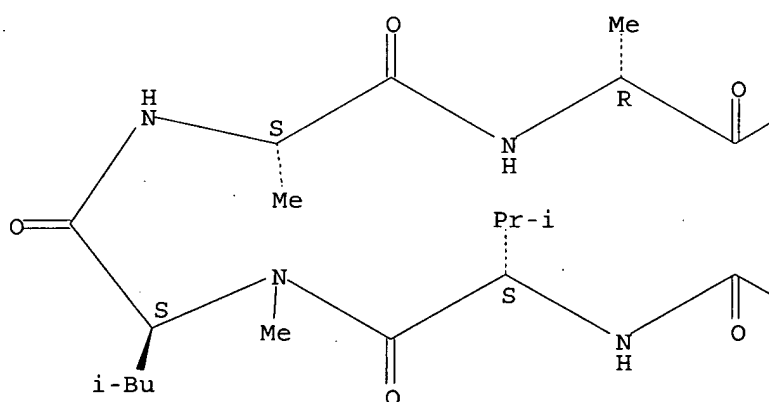


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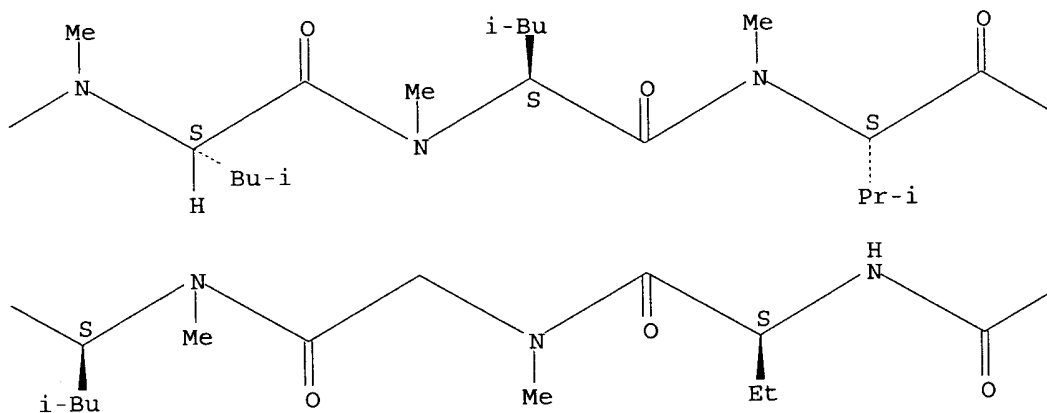
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Absolute stereochemistry.

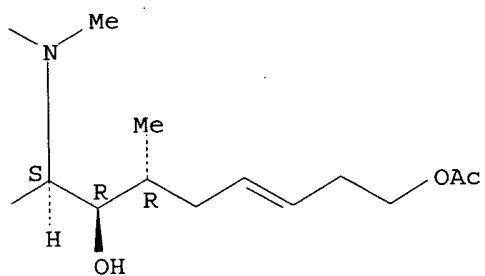
Double bond geometry unknown.



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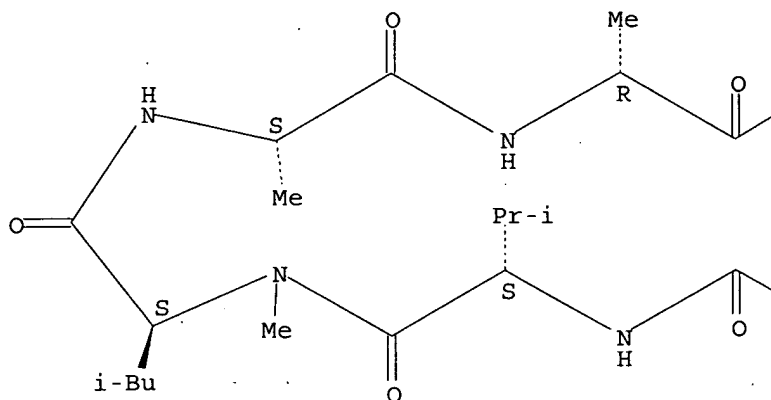
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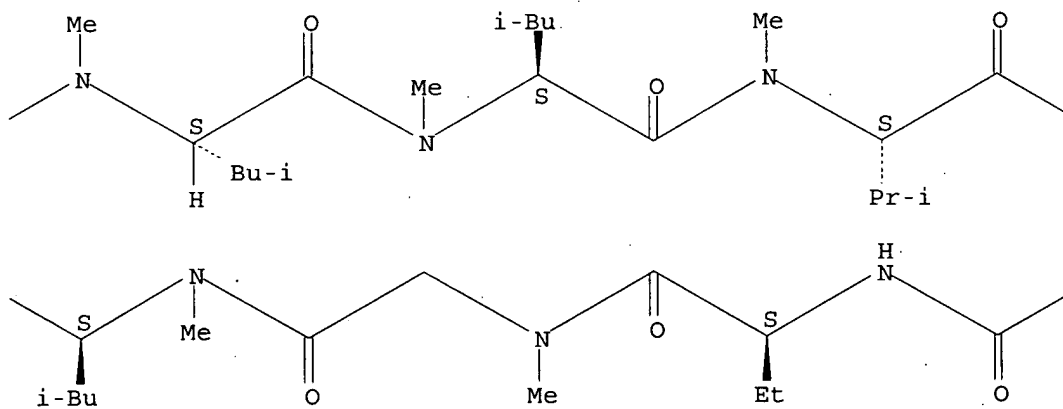
RN 700371-72-8 HCAPLUS
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 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

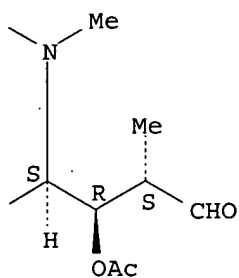
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IT 114865-25-7P 699022-27-0P 699022-29-2P

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 699022-38-3P 699022-39-4P 699022-40-7P
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 699022-51-0P 700371-73-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

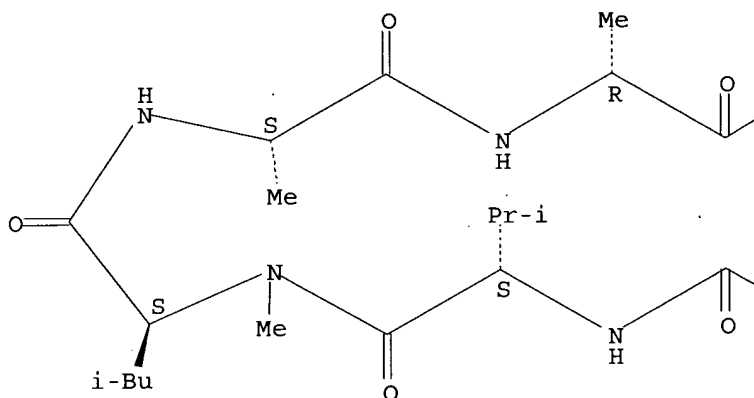
(preparation of **cyclosporins** for treatment of immune disorders)

RN 114865-25-7 HCAPLUS

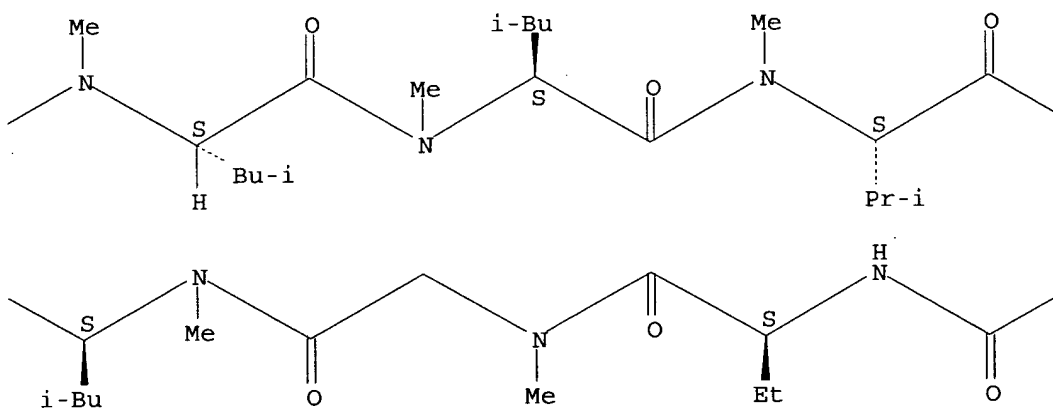
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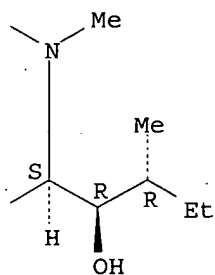
Absolute stereochemistry.

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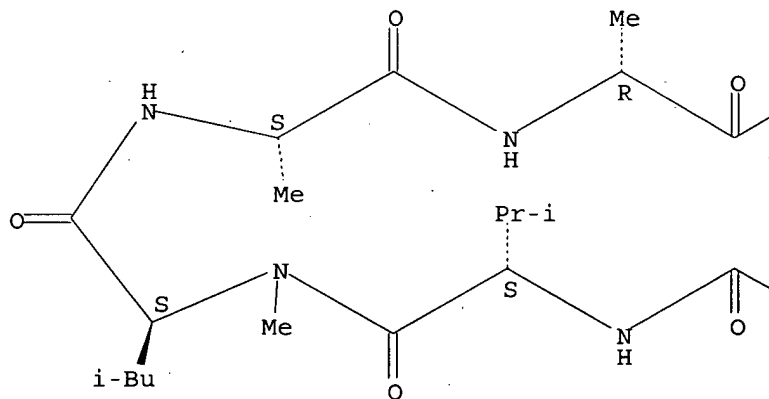




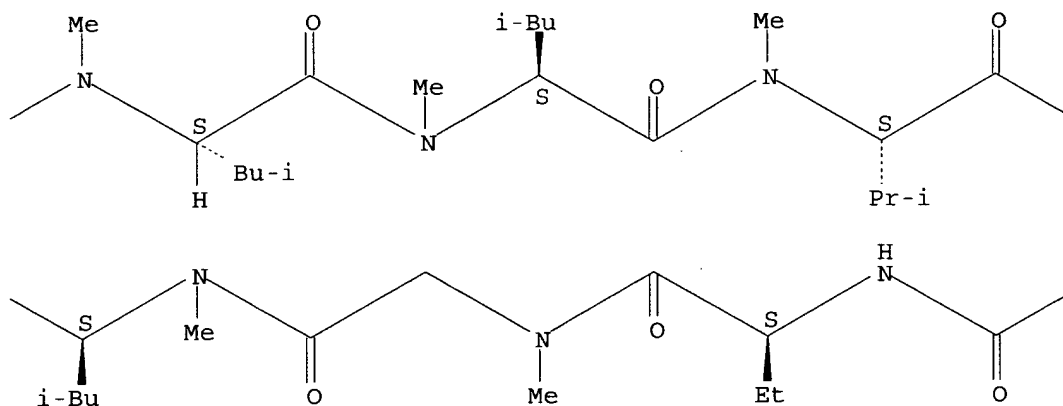
RN 699022-27-0 HCAPLUS

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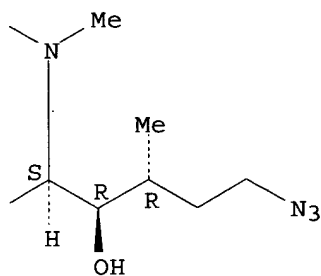
Absolute stereochemistry.



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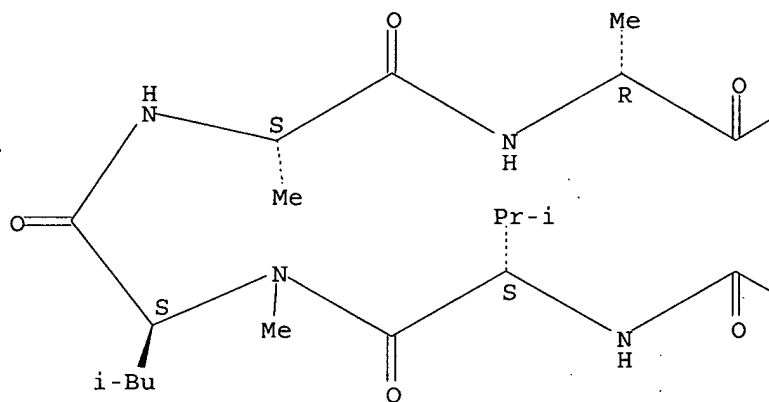


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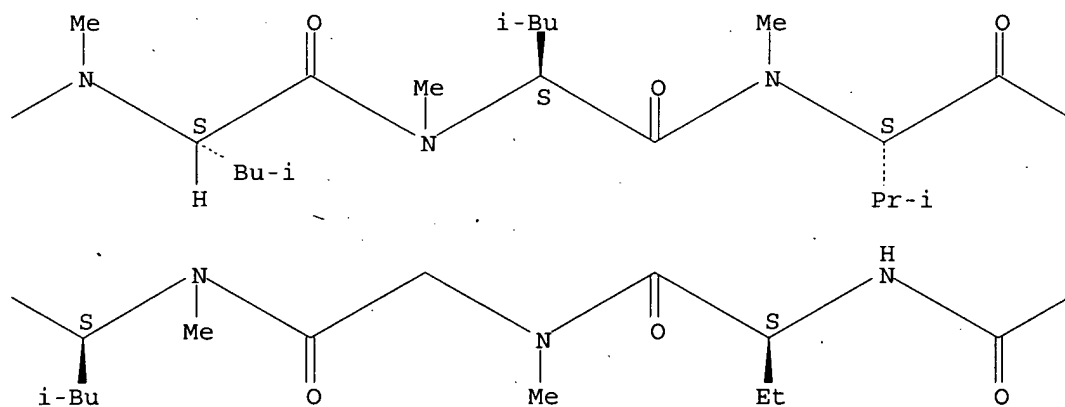
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Absolute stereochemistry.

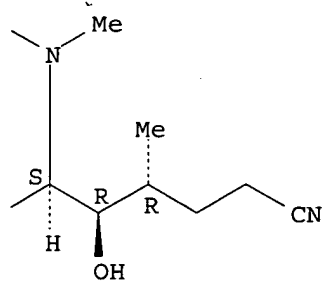
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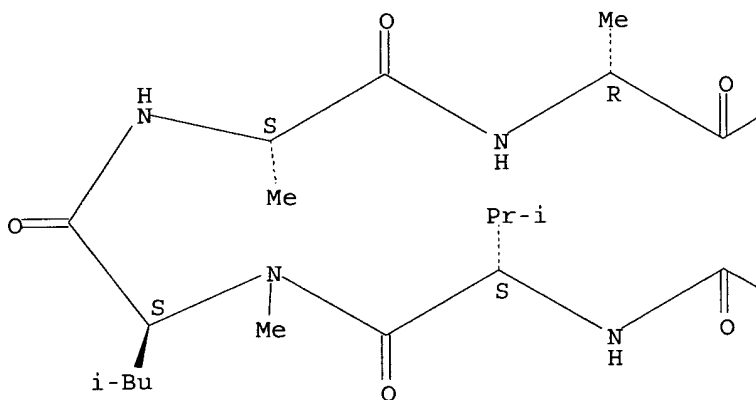


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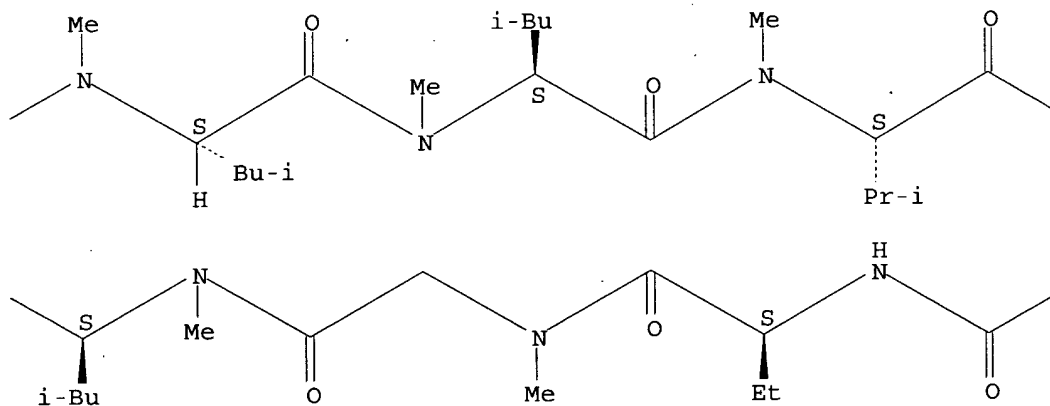
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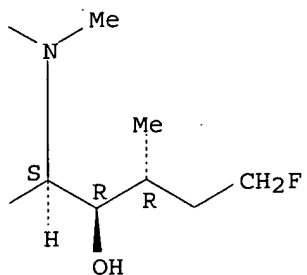
Absolute stereochemistry.

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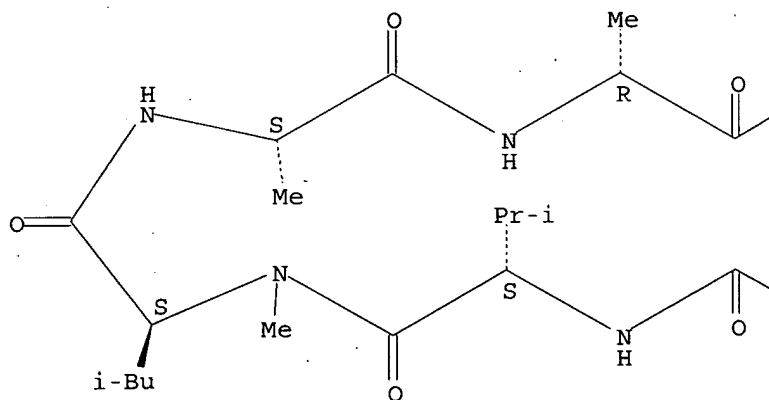




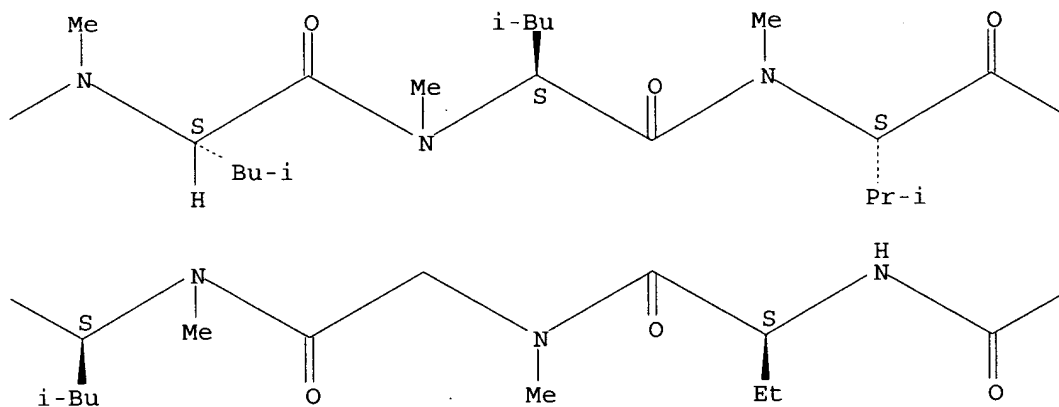
RN 699022-33-8 HCAPLUS

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(9CI) (CA INDEX NAME)

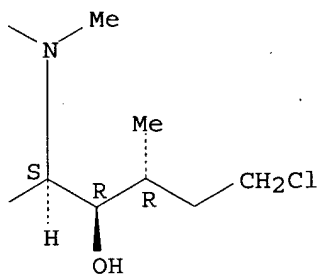
Absolute stereochemistry.



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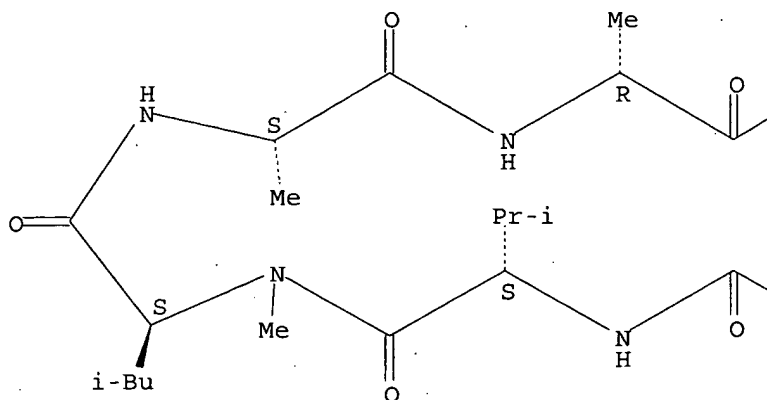


RN 699022-34-9 HCAPLUS

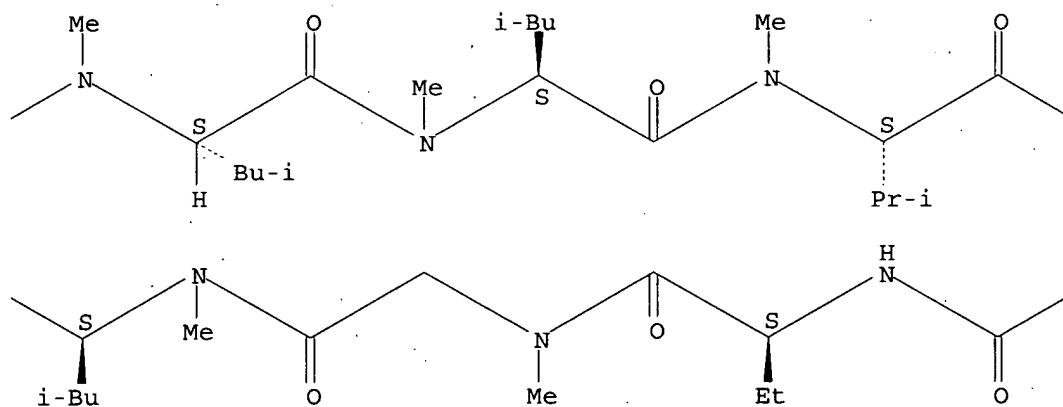
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Absolute stereochemistry.

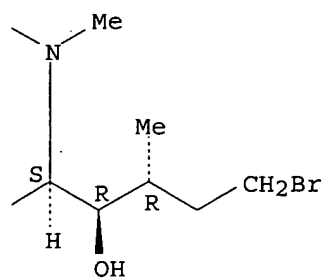
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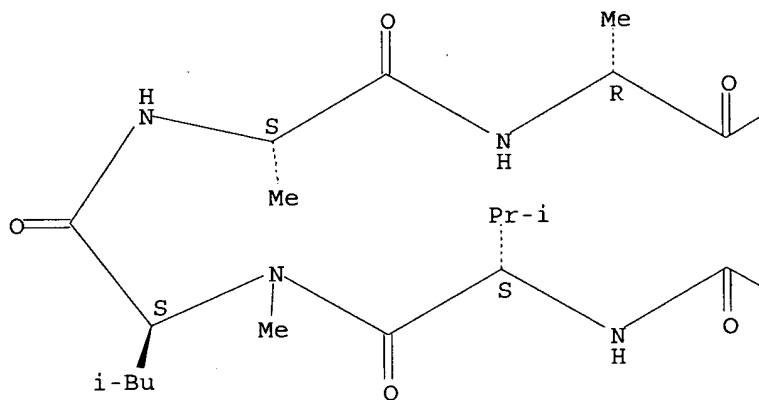


RN 699022-38-3 HCAPLUS

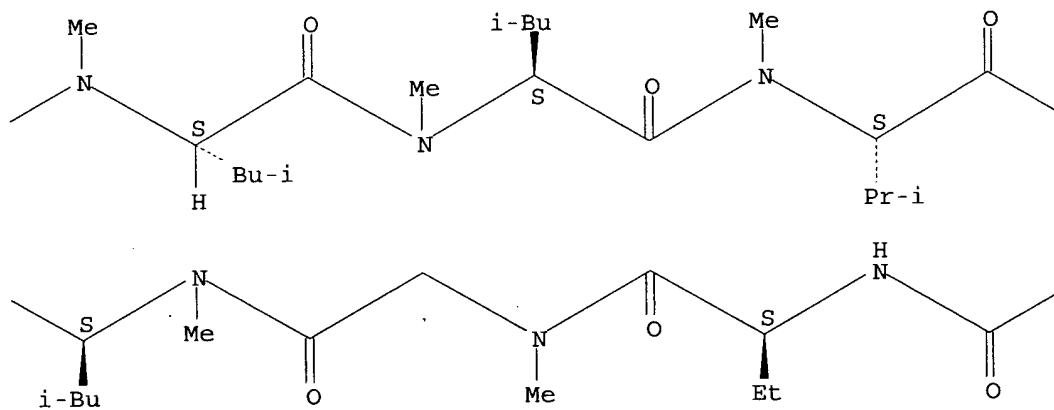
CN Cyclosporin A, 6-[3-O-acetyl-2,4-dideoxy-4-methyl-2-(methylamino)-5-O-(methylsulfonyl)-D-arabinonic acid]- (9CI) (CA INDEX NAME)

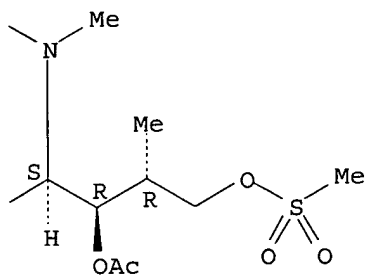
Absolute stereochemistry.

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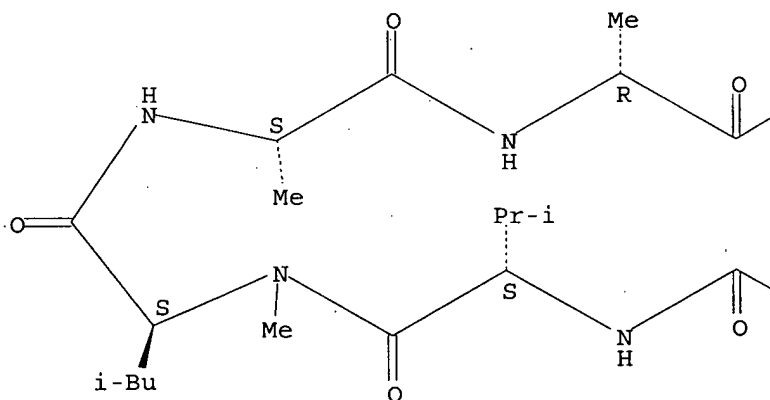




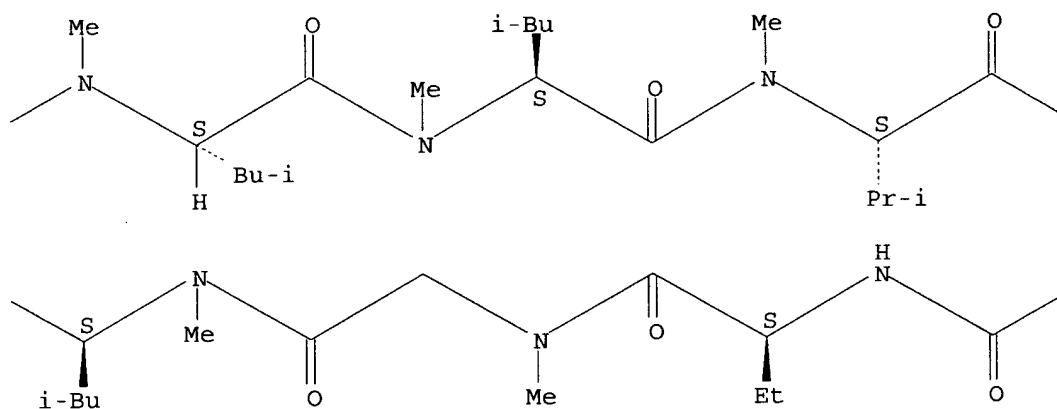
RN 699022-39-4 HCAPLUS

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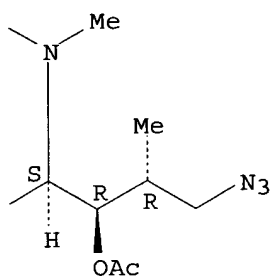
Absolute stereochemistry.



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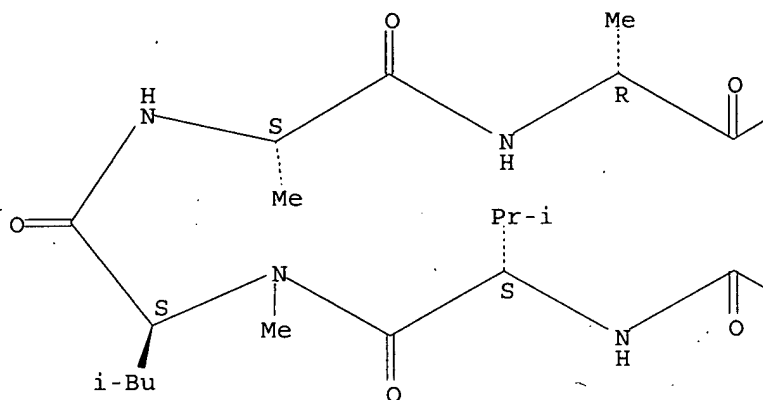


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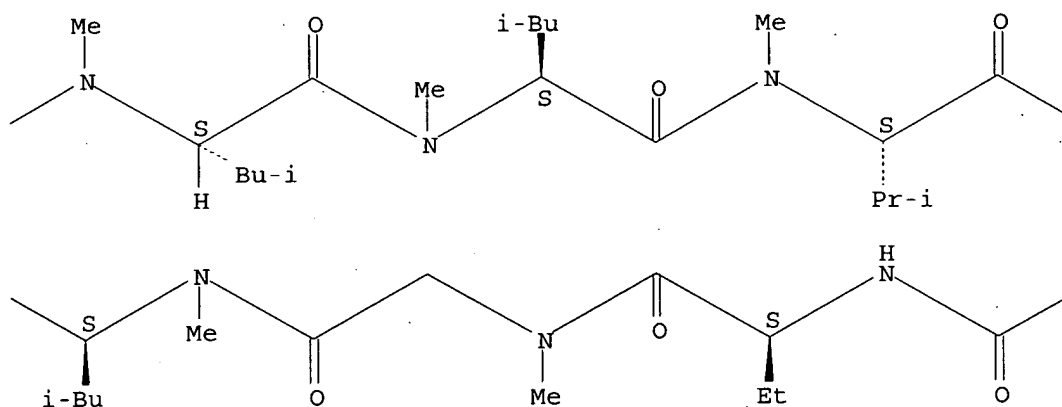
CN Cyclosporin A, 6-[5-azido-2,4,5-trideoxy-4-methyl-2-(methylamino)-D-arabinonic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

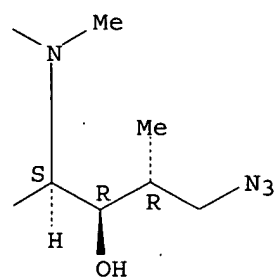
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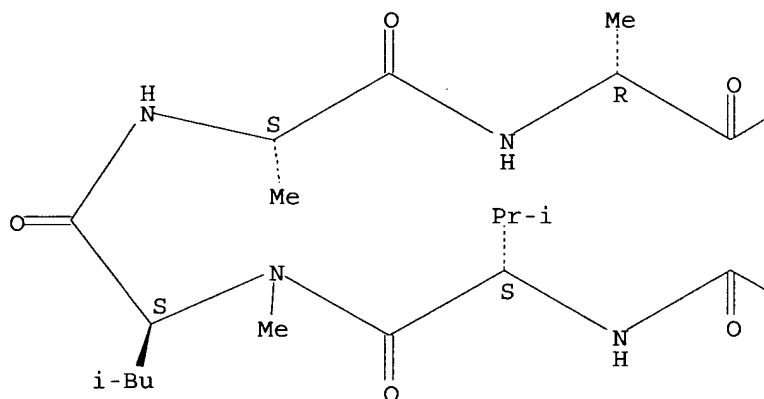


RN 699022-41-8 HCAPLUS

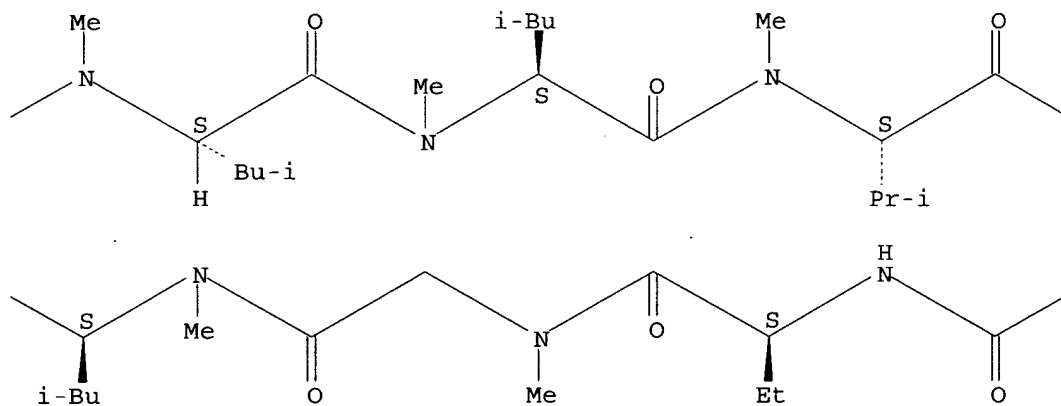
CN Cyclosporin A, 6-[(3R,4R)-5-cyano-3-hydroxy-N-methyl-L-leucine]- (9CI)
(CA INDEX NAME)

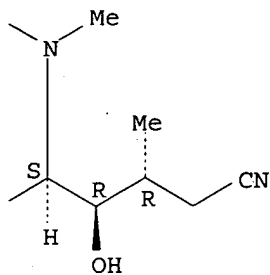
Absolute stereochemistry.

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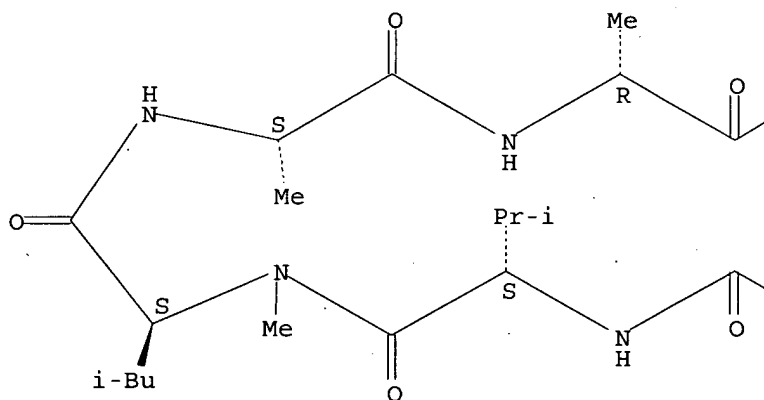




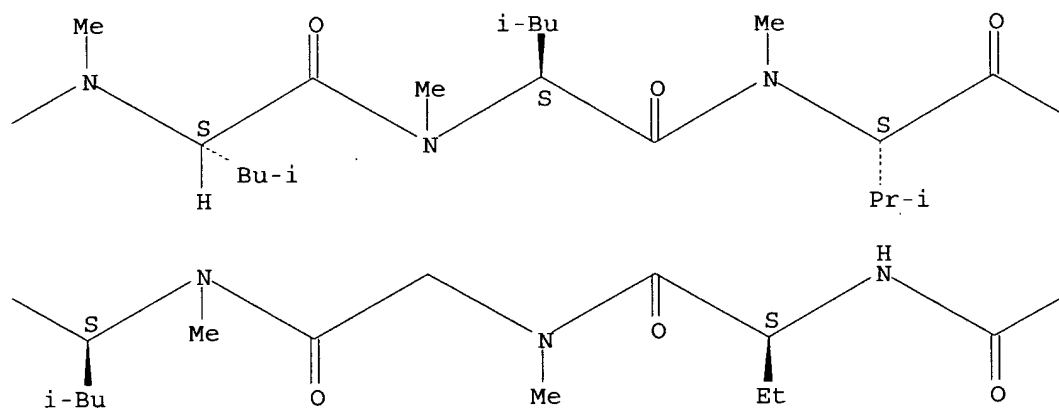
RN 699022-42-9 HCAPLUS

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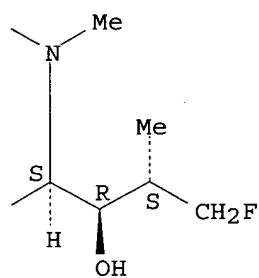
Absolute stereochemistry.



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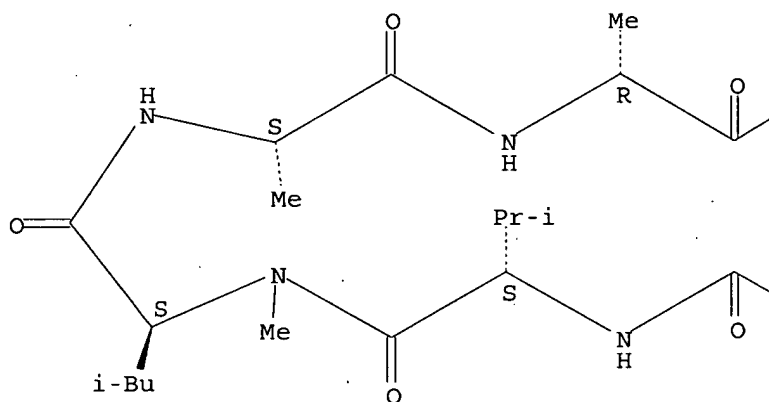
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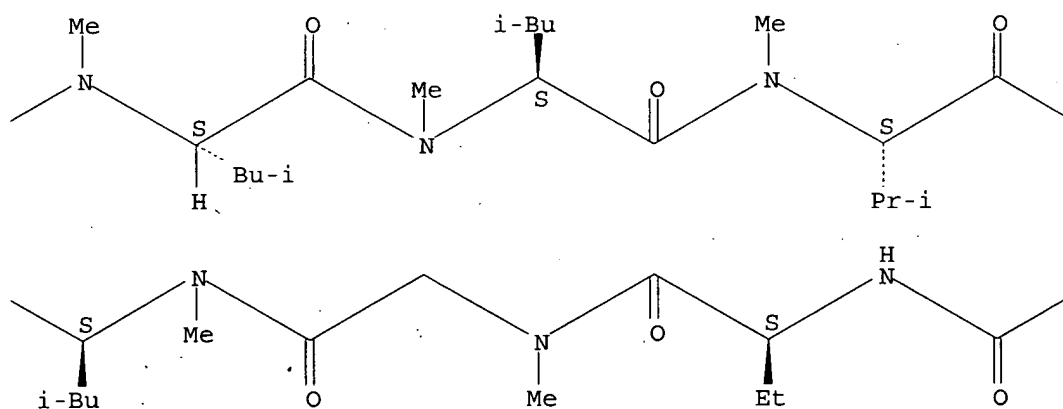
RN 699022-43-0 HCAPLUS
 CN Cyclosporin A, 6-[(3R,4R)-5,6-didehydro-3-hydroxy-N,4-dimethyl-L-norleucine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

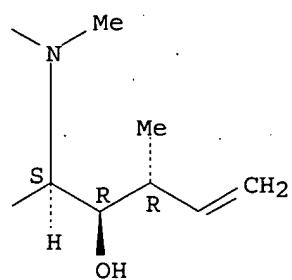
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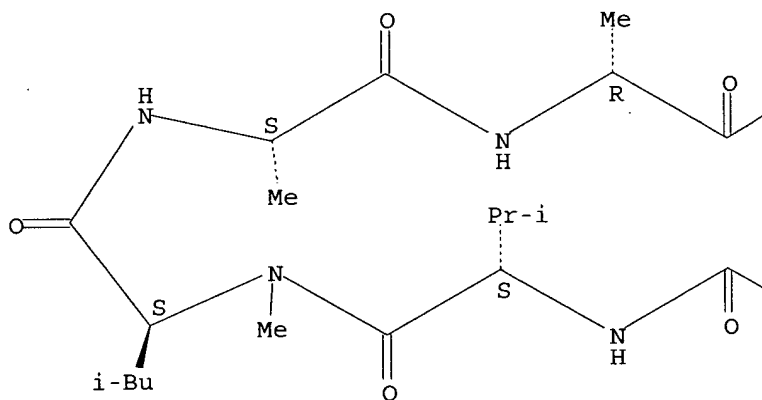


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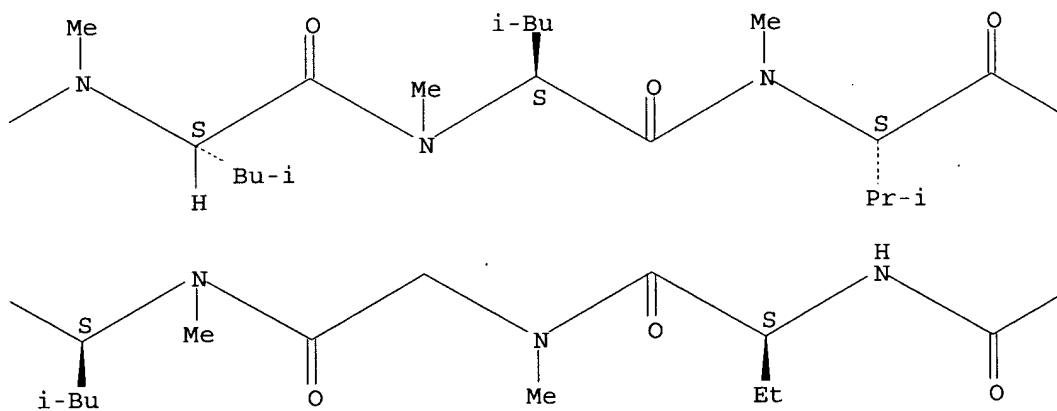
CN Cyclosporin A, 6-[(2S,3R,4R)-10-(acetyloxy)-3-hydroxy-4-methyl-2-(methylamino)-6-decenoic acid]- (9CI) (CA INDEX NAME)

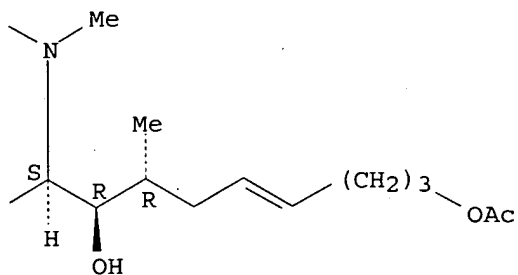
Absolute stereochemistry.
Double bond geometry unknown.

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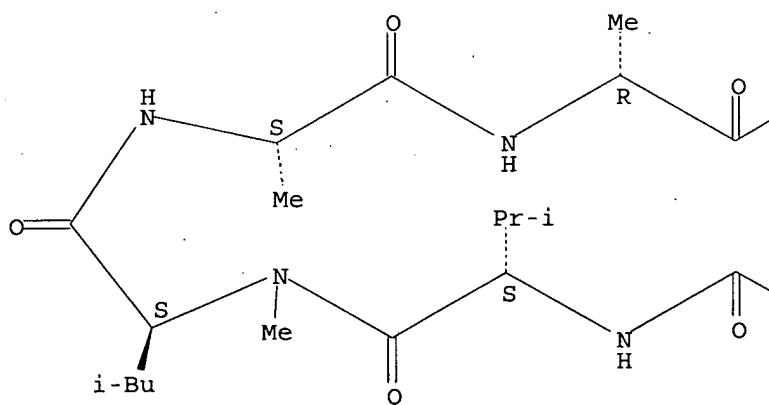


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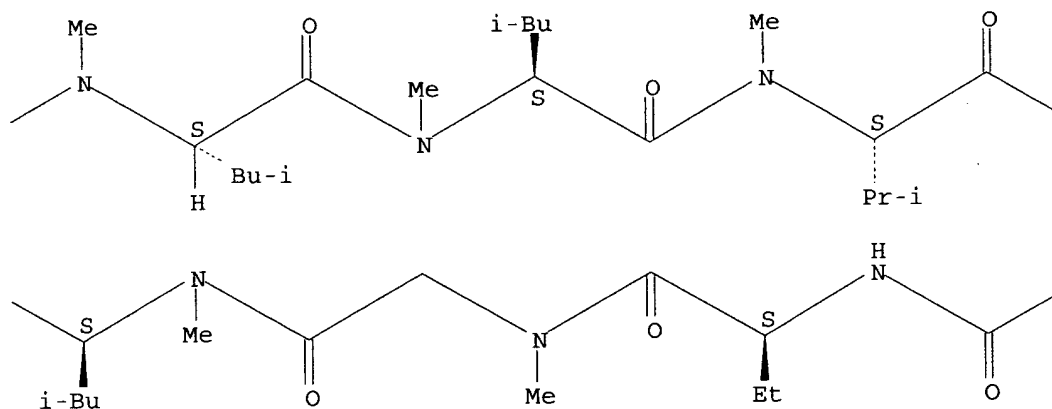
CN Cyclosporin A, 6-[(2S,3R,4R)-11-(acetyloxy)-3-hydroxy-4-methyl-2-(methylamino)-6-undecenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

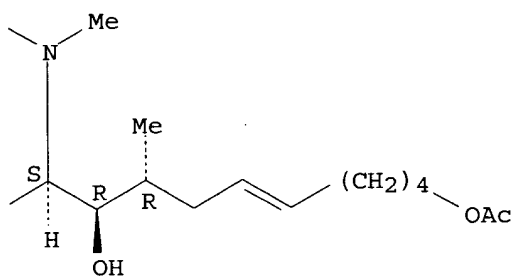
Double bond geometry unknown.



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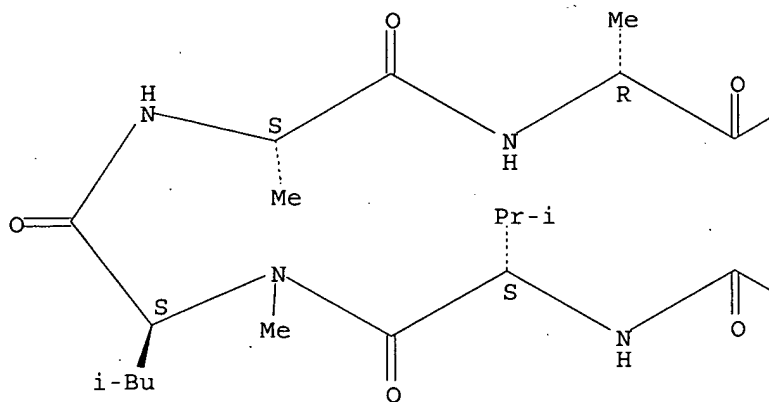


RN 699022-47-4 HCAPLUS

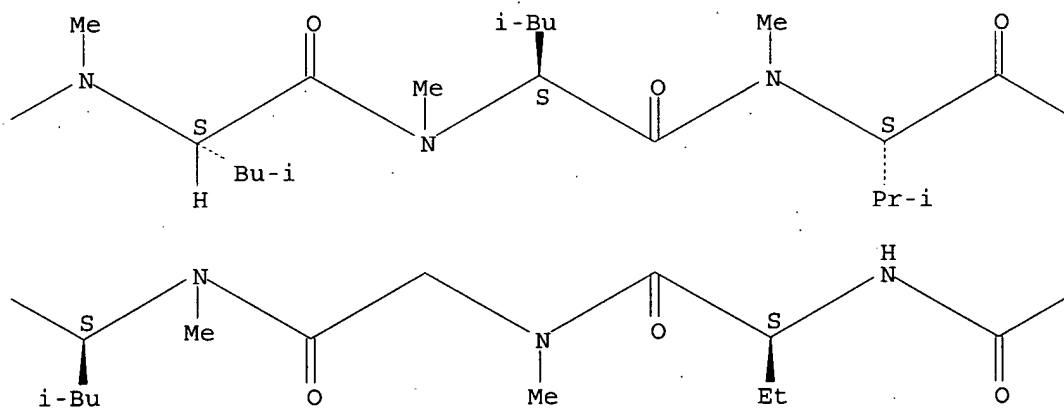
CN Cyclosporin A, 6-[(2S,3R,4R)-10-cyano-3-hydroxy-4-methyl-2-(methylamino)-6-decenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

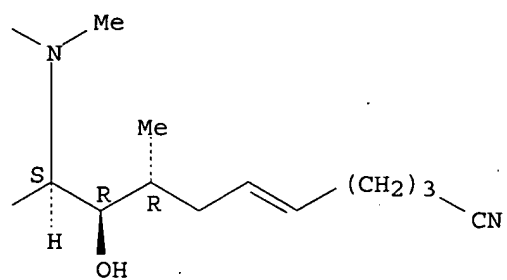
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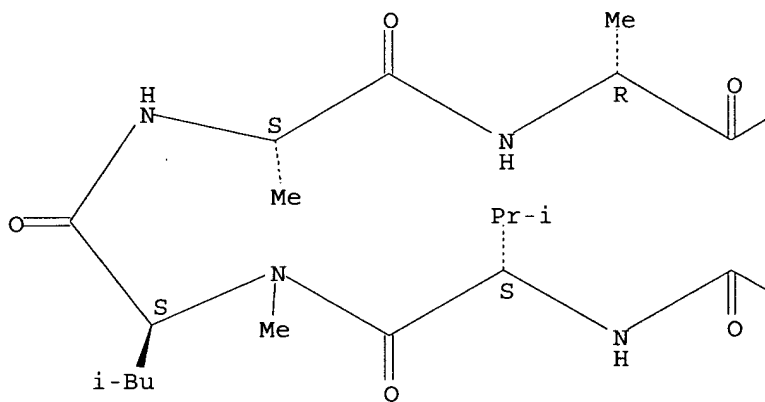


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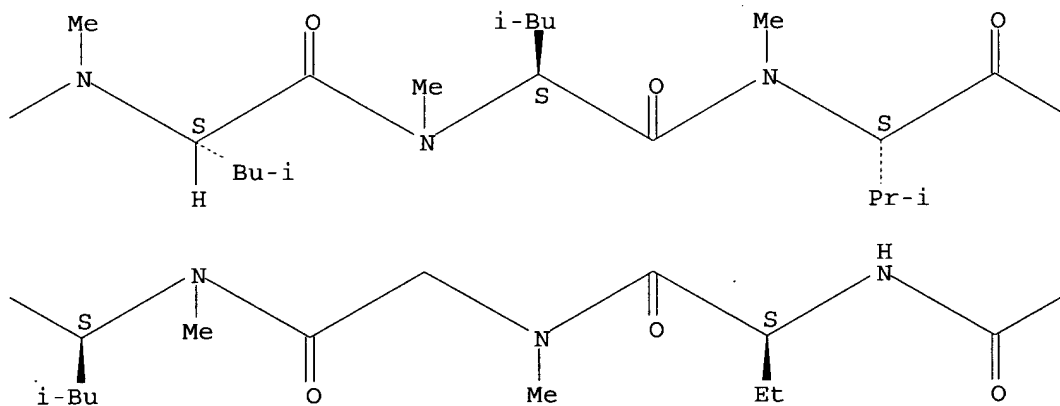
CN Cyclosporin A, 6-[5-chloro-2,4,5-trideoxy-4-methyl-2-(methylamino)-D-arabinonic acid]- (9CI) (CA INDEX NAME)

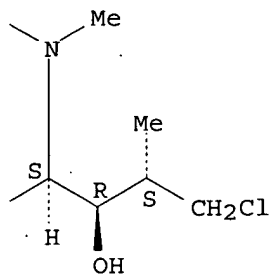
Absolute stereochemistry.

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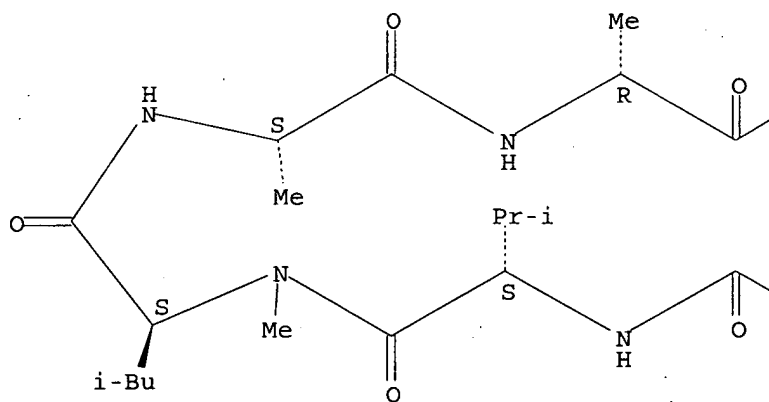




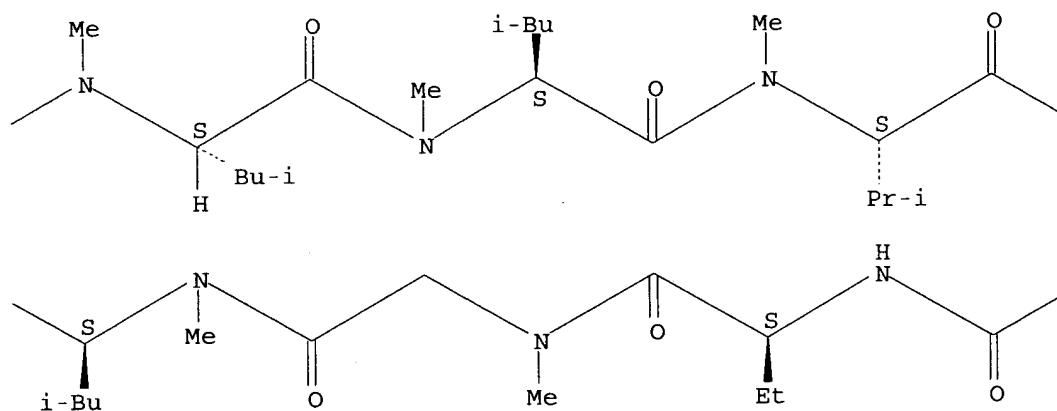
RN 699022-49-6 HCAPLUS

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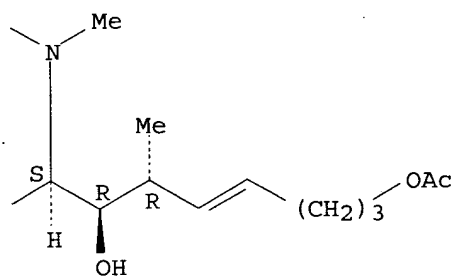
Absolute stereochemistry.
Double bond geometry unknown.



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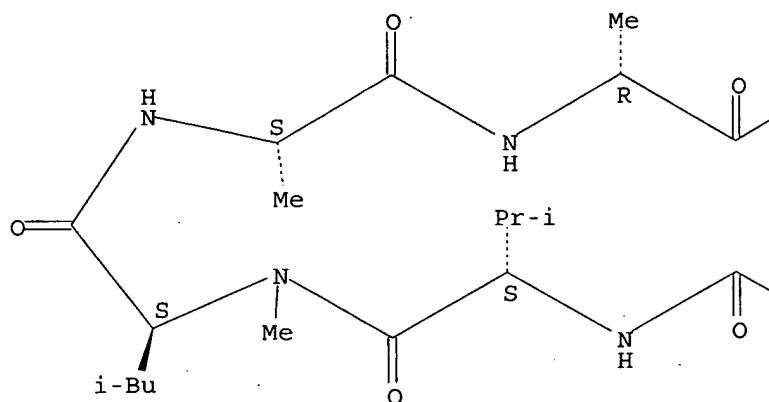


RN 699022-50-9 HCAPLUS

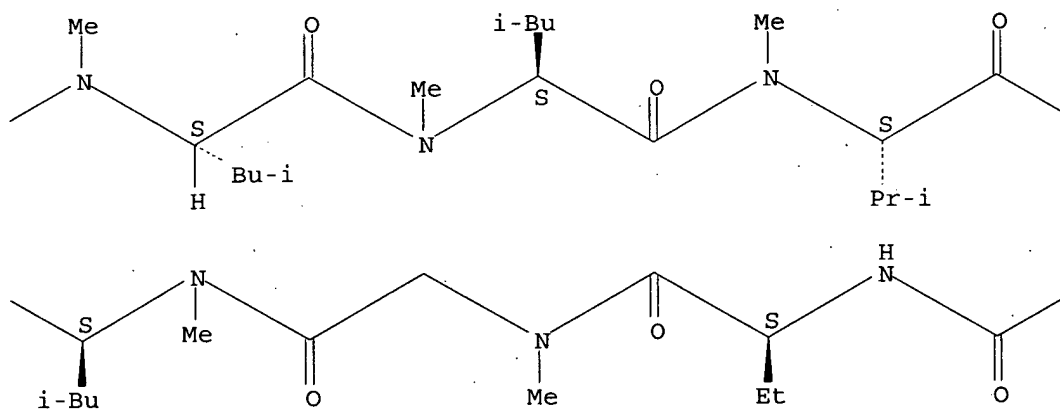
CN Cyclosporin A, 6-[(2S,3R,4R)-10-azido-3-hydroxy-4-methyl-2-(methylamino)-6-decenoic acid] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

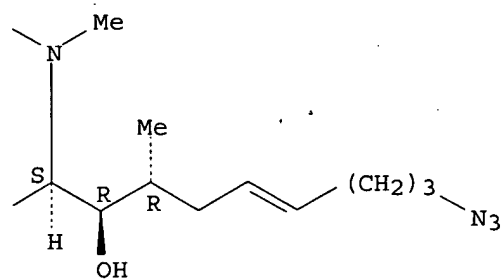
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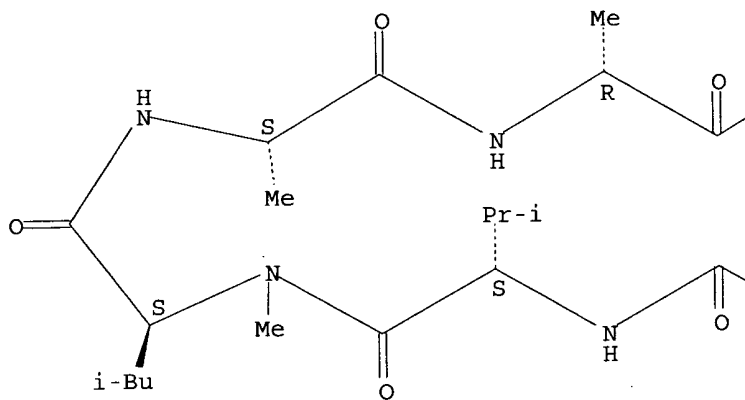


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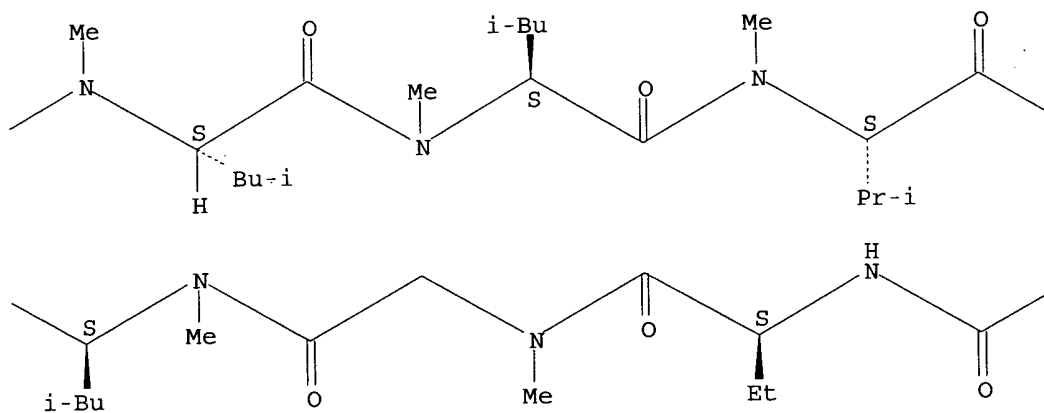
CN Cyclosporin A, 6-[(3R,4S)-3-hydroxy-N-methyl-5-oxo-L-leucine] - (9CI) (CA
INDEX NAME)

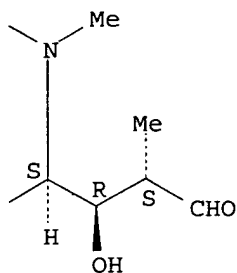
Absolute stereochemistry.

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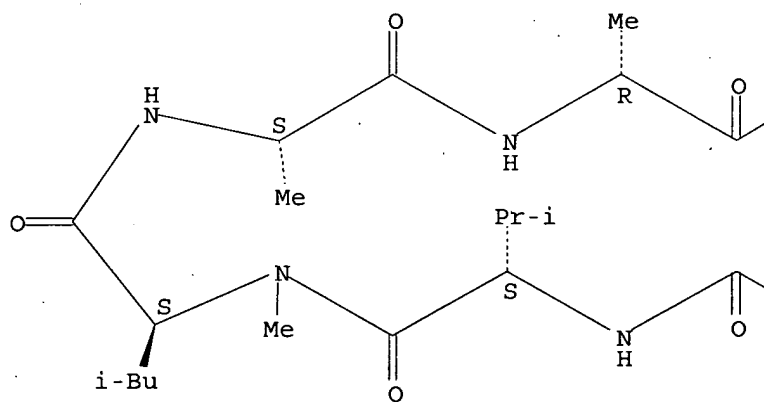




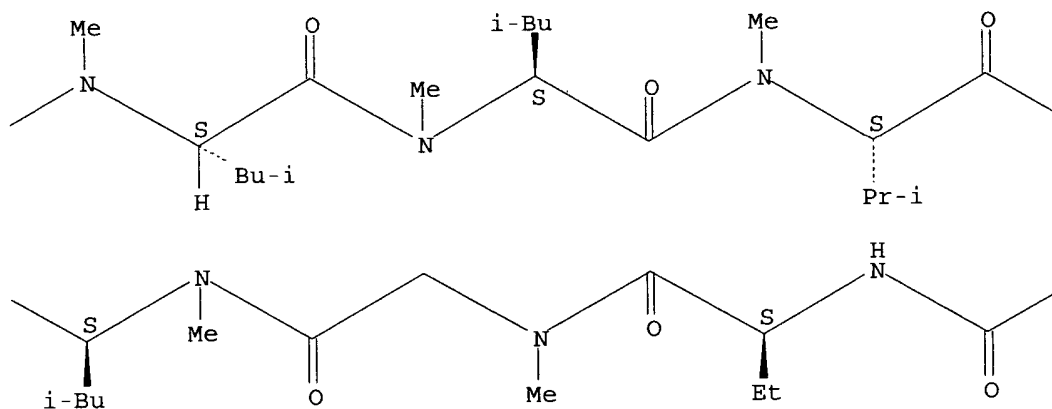
RN 700371-73-9 HCAPLUS

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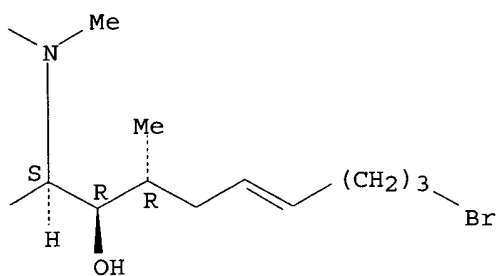
Absolute stereochemistry.
Double bond geometry unknown.



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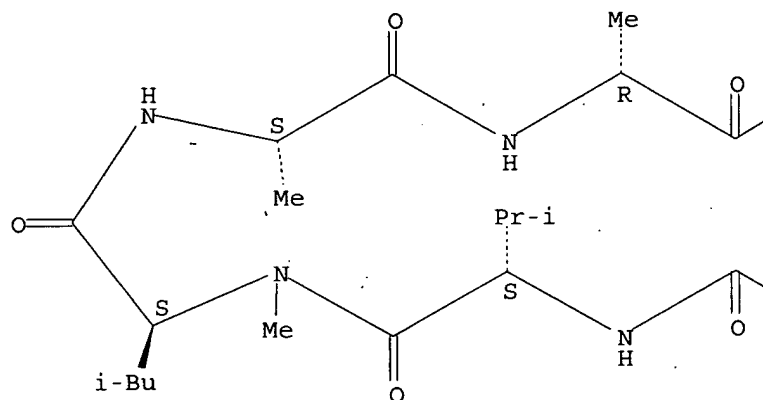
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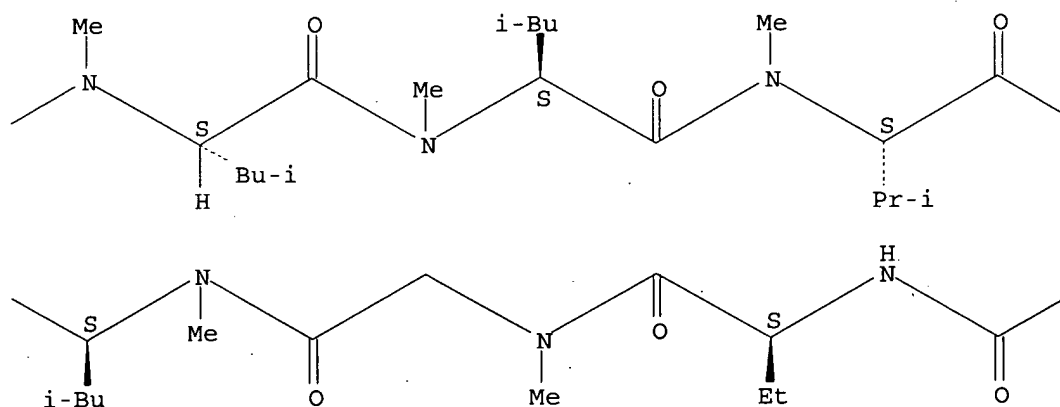
IT 59865-13-3, Cyclosporin a
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of cyclosporins for treatment of immune disorders)
 RN 59865-13-3 HCAPLUS
 CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

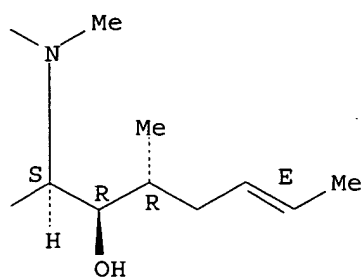
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L17 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:777363 HCAPLUS
 DOCUMENT NUMBER: 139:277169
 TITLE: Preparation of **cyclosporins** for the
 treatment of immune disorders
 INVENTOR(S): **Or, Yat Sun**; Lazarova, Tsvetelina; Eckstein,
 Jens Werner
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S.
 Ser. No. 800,856.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003186855	A1	20031002	US 2003-349890	20030123
US 2002142946	A1	20021003	US 2001-800856	20010305
US 6784156	B2	20040831		
US 2003109426	A1	20030612	US 2003-345866	20030116
PRIORITY APPLN. INFO.:			US 2001-800856	A2 20010305

OTHER SOURCE(S): MARPAT 139:277169

AB The invention relates to **cyclosporins** cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is -NMeCH[CH(OH)CHMeCH₂CH:CH-X-Y]CO- of stereo α S, β R, γ R, where X is absent or (cyclo)alkyl and Y is (thio)carboxy or (un)substituted alkyl ester; B is - α Abu-, -Val-, -Thr- or -Nva-; U is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-, -[O-acyl-D-Ser]- or -[O-(2-acyloxyethyl)-D-Ser]-] and their prodrugs or pharmaceutically-acceptable salts for treating or preventing an inflammatory or immune disorder while eliminating or reducing the toxicity associated with administration of **cyclosporin A**. The synthesis of analogs I involves modification of residue -NMeCH[CH(OH)CHMeCH₂CH:CHMe]CO- (same stereo) by reaction with CH₂:CH-X-Y. Thus, I (X is absent, Y is CO₂Me, B is - α Abu-, and U is -D-Ala-) was prepared by treatment of **cyclosporin A** with Me acrylate over Nolan catalyst. Calcineurin inhibition assay IC₅₀ values were determined at inhibitor concns. 20 to 0.006 μ M.

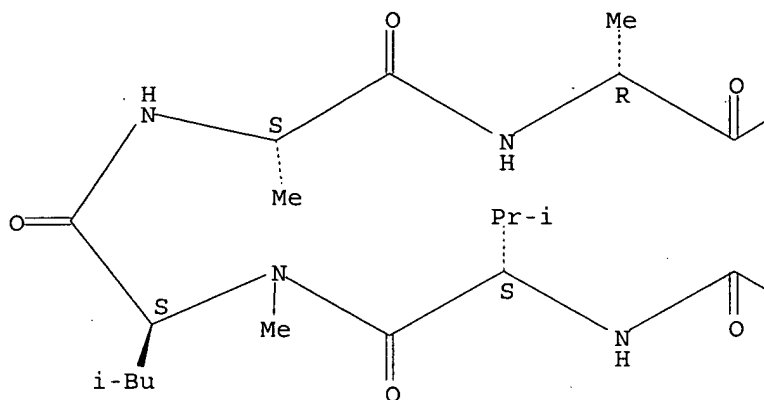
IT **122547-85-7P**
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (preparation of **cyclosporins** for the treatment of immune disorders)

RN 122547-85-7 HCAPLUS

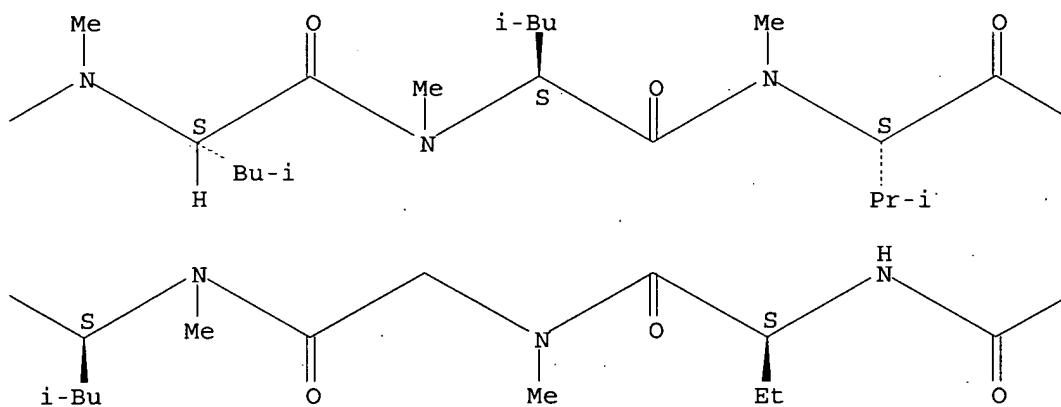
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

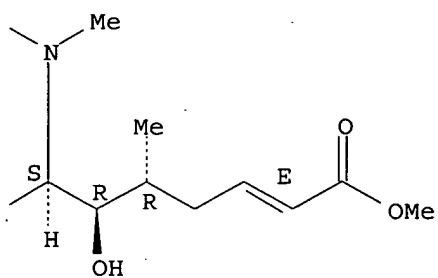
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IT 100364-58-7P 457612-98-5P 457613-00-2P

457613-01-3P 457613-10-4P 457613-11-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

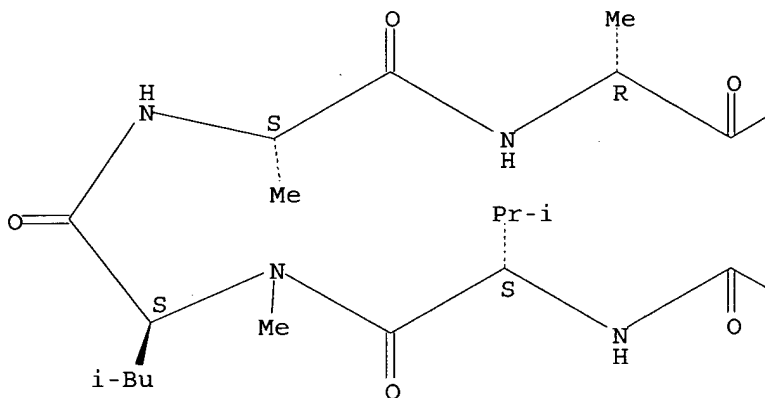
(preparation of **cyclosporins** for the treatment of immune disorders)

RN 100364-58-7 HCAPLUS

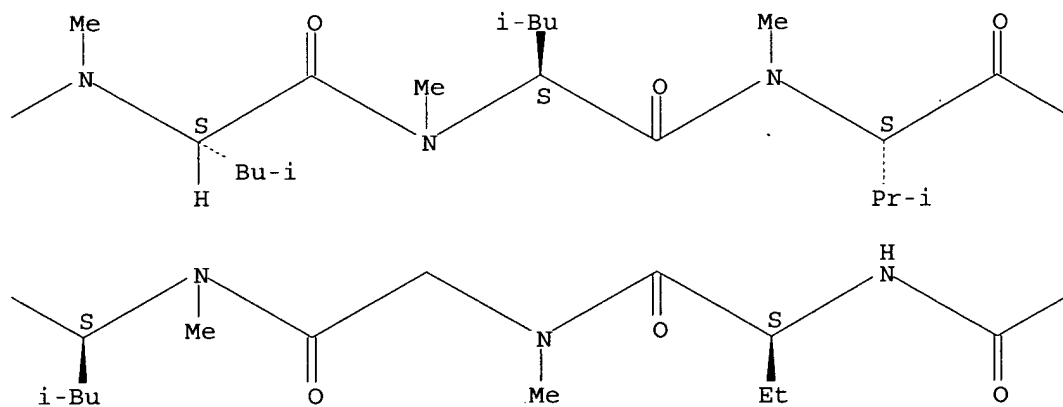
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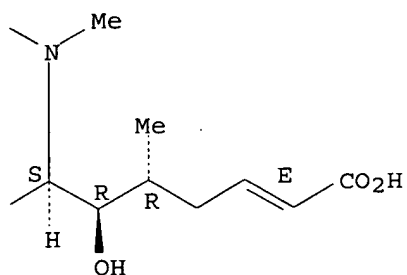
Absolute stereochemistry.
Double bond geometry as shown.

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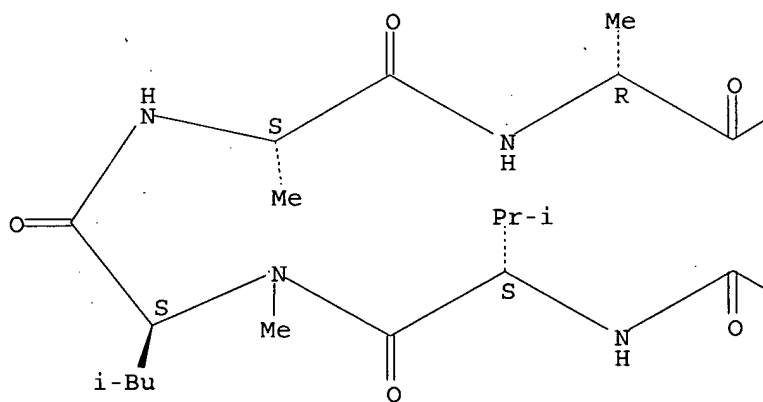




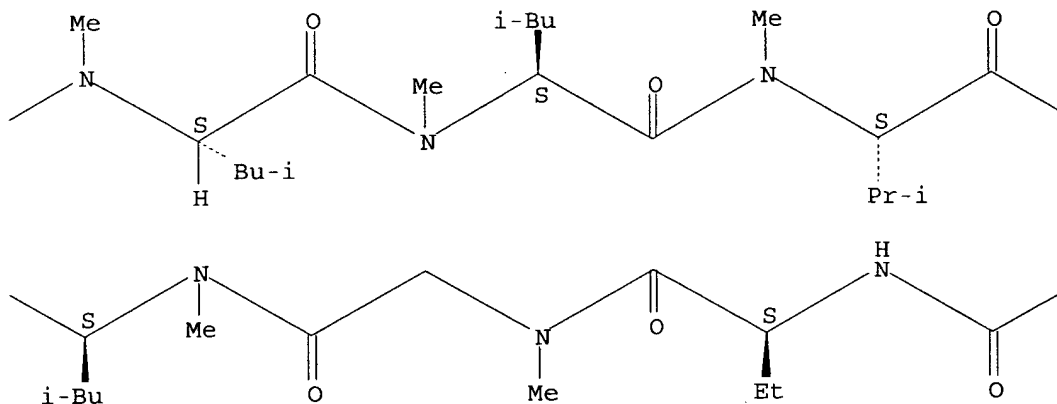
RN 457612-98-5 HCAPLUS

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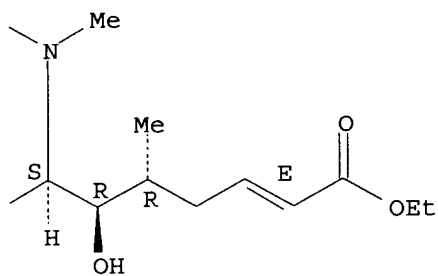
Absolute stereochemistry.
Double bond geometry as shown.



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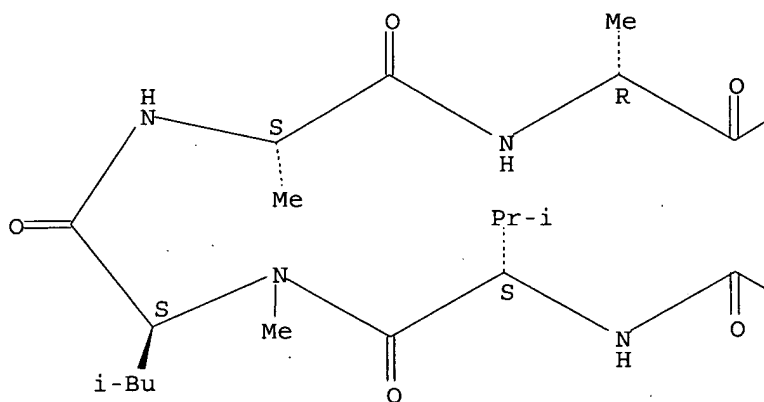


RN 457613-00-2 HCAPLUS

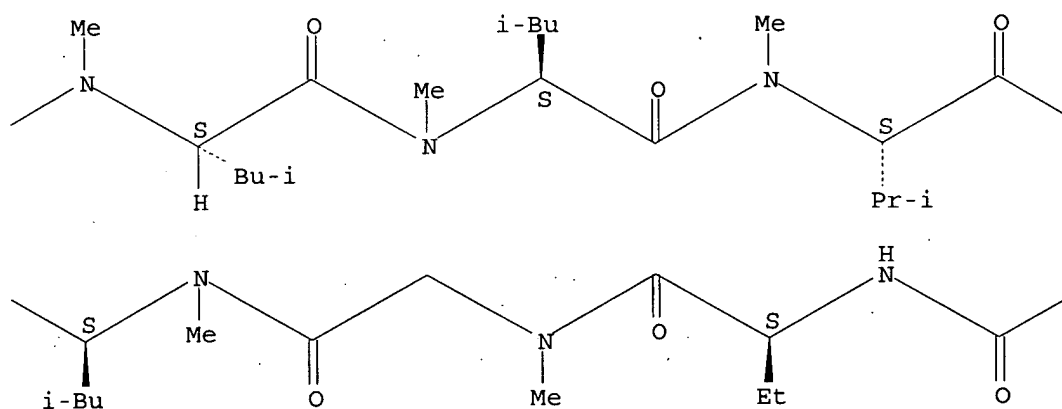
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

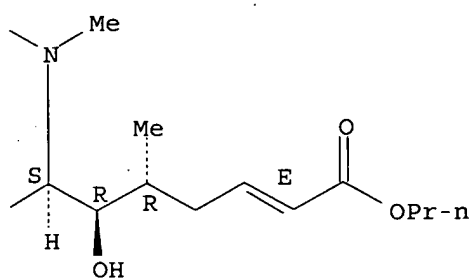
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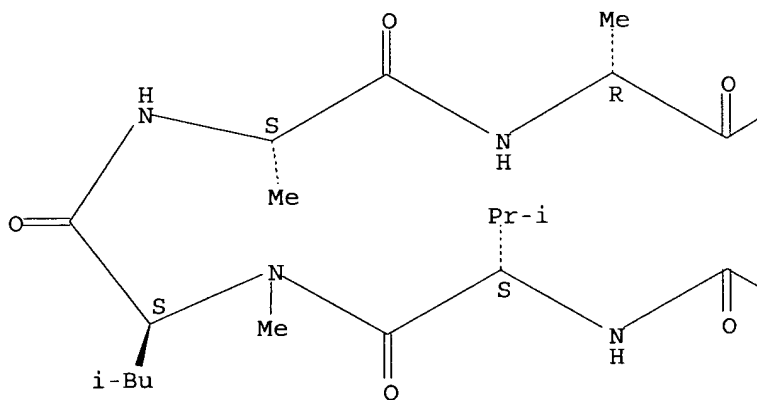


RN 457613-01-3 HCAPLUS

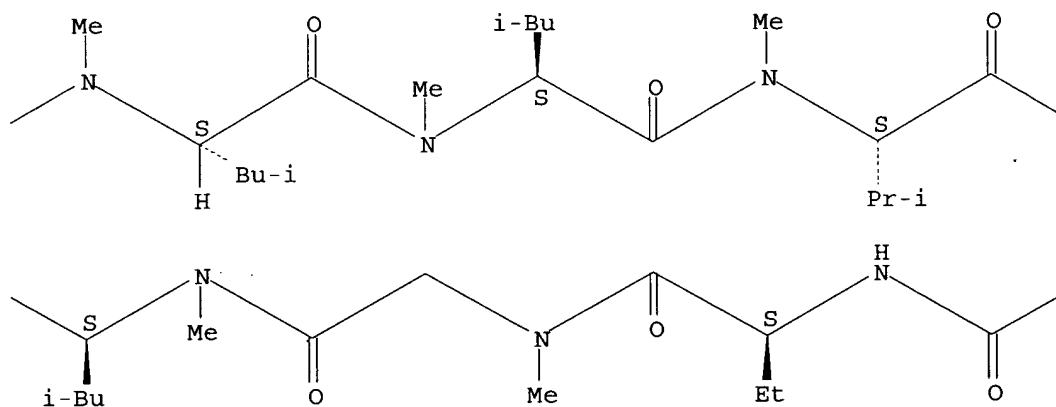
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, phenylmethyl ester (9CI) (CA INDEX NAME)

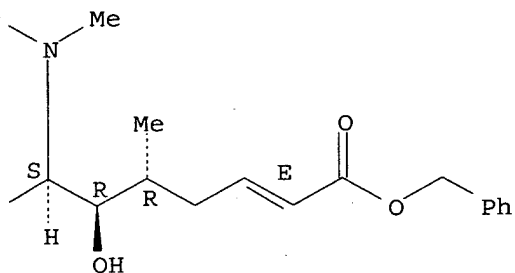
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

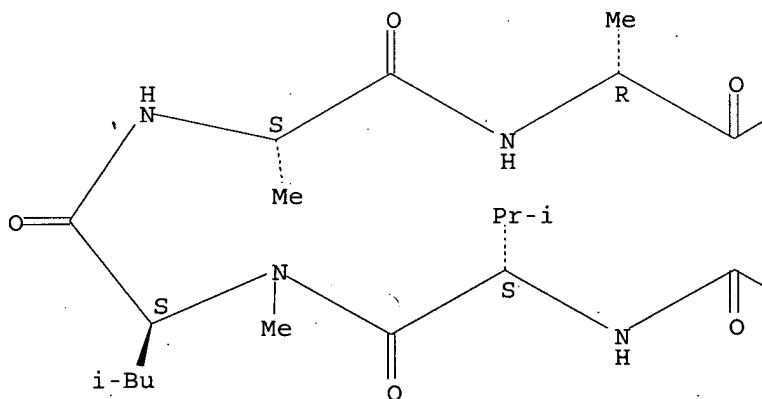




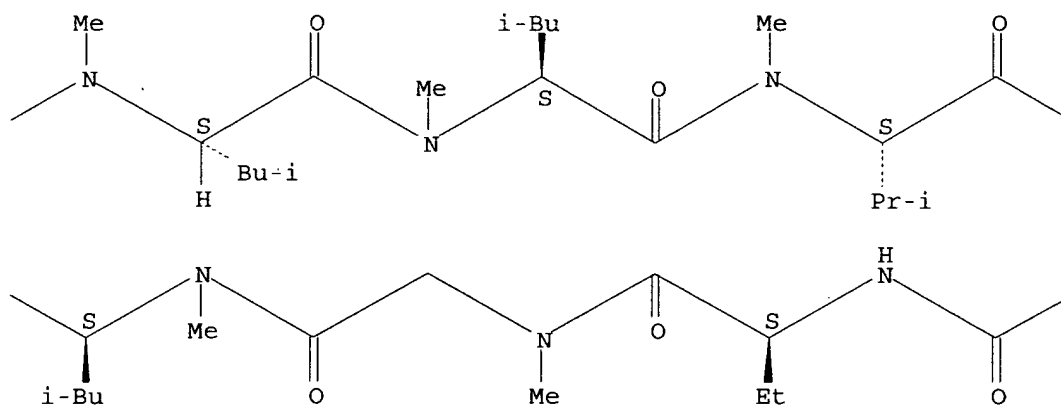
RN 457613-10-4 HCAPLUS

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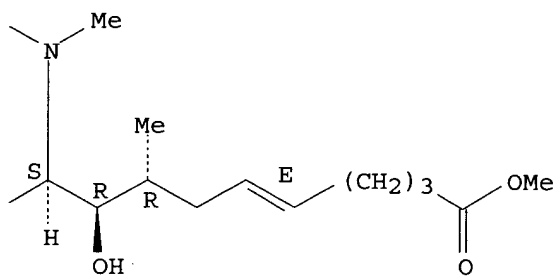
Absolute stereochemistry.
Double bond geometry as shown.



PAGE 1-B



PAGE 1-C

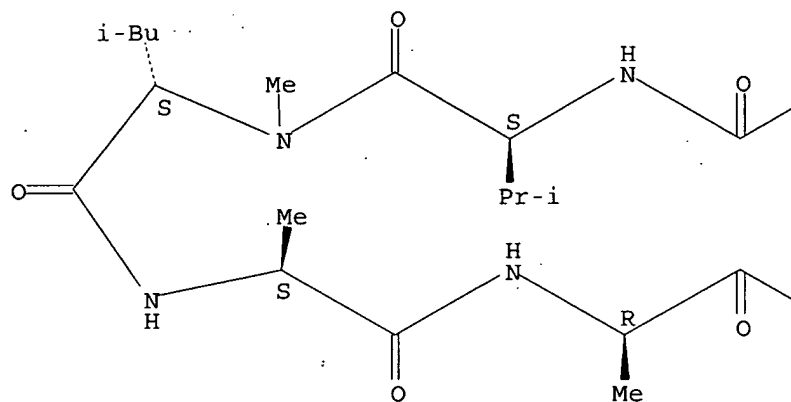


RN 457613-11-5 HCAPLUS

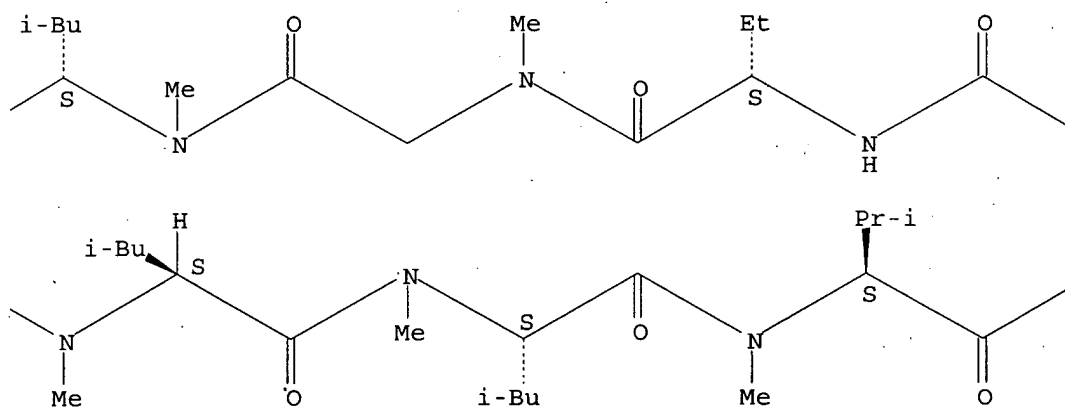
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

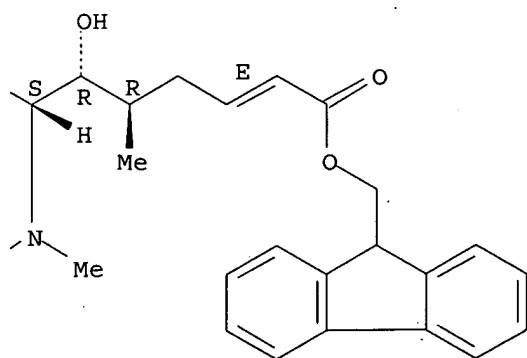
PAGE 1-A



PAGE 1-B



PAGE 1-C



IT 59865-13-3, Cyclosporin a

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of cyclosporins for the treatment of immune disorders)

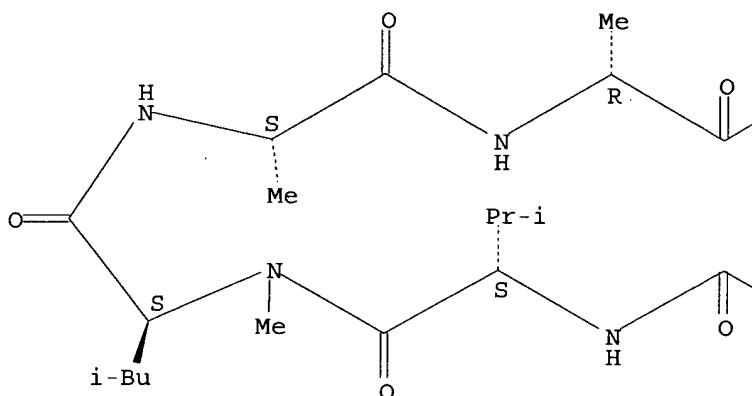
RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

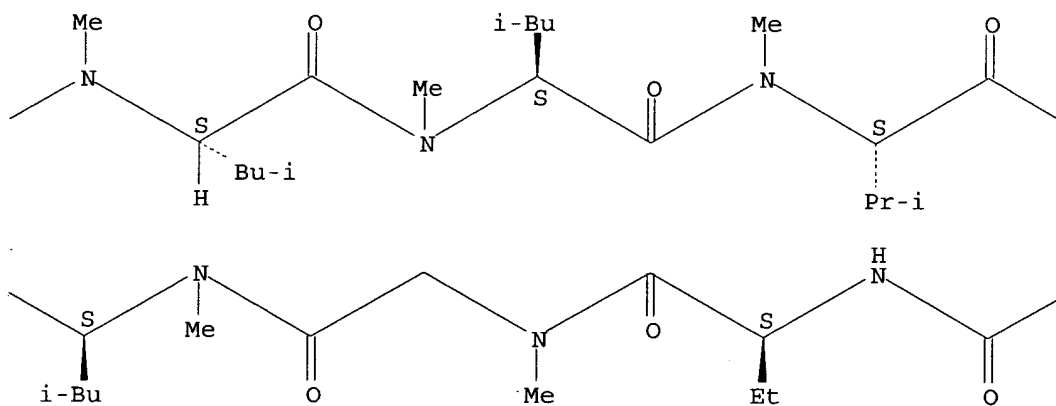
Absolute stereochemistry.

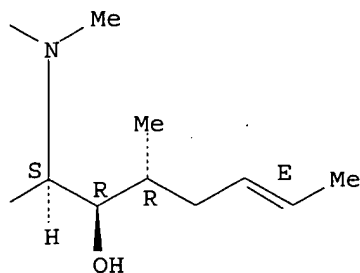
Double bond geometry as shown.

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PAGE 1-B





L17 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:696512 HCAPLUS

DOCUMENT NUMBER: 139:214721

TITLE: Preparation of cyclosporin analogs for the treatment of immune disorders

INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Eckstein, Jens Werner

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Pat. Appl. 2003 87,813.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003166515	A1	20030904	US 2003-349877	20030123
US 6979671	B2	20051227		
US 2003087813	A1	20030508	US 2001-975923	20011012
US 2003109425	A1	20030612	US 2003-345855	20030116
PRIORITY APPLN. INFO.:			US 2001-975923	A2 20011012

OTHER SOURCE(S): CASREACT 139:214721; MARPAT 139:214721

AB The invention relates to cyclosporin analogs cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is -NMeCH[CH(OH)CHMe(CH₂)₃-X-Y]CO- of stereo α S, β R, γ R, where X is absent or (cyclo)alkyl and Y is (thio)carboxy or (un)substituted alkyl ester; B is - α Abu-, -Val-, -Thr- or -Nva-; U is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-, -[O-acyl-D-Ser]- or -[O-(2-acyloxyethyl)-D-Ser]-] and their prodrugs or pharmaceutically-acceptable salts for treating or preventing an inflammatory or immune disorder while eliminating or reducing the toxicity associated with administration of cyclosporin A. The synthesis of analogs I involves modification of residue -NMeCH[CH(OH)CHMeCH₂CH:CHMe]CO- (A', same stereo) by reaction with CH₂:CH-X-Y, followed by catalytic hydrogenation. Thus, I (X is absent, Y is CO₂Me, B is - α Abu-, and U is -D-Ala-) was prepared by hydrogenation of cyclosporin Me ester over Pd/C. Compds. of the invention showed IC₅₀ values 0.1 to 0.0015 μ M for inhibition of calcineurin.

IT 502998-21-2P 502998-23-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

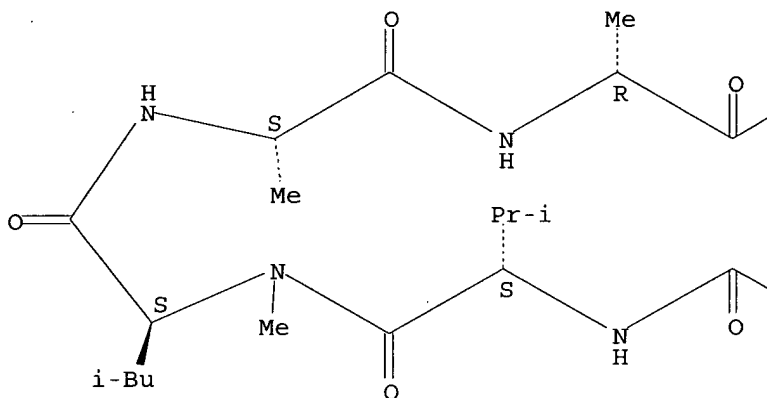
(preparation of cyclosporin analogs for treatment of immune disorders)

RN 502998-21-2 HCAPLUS

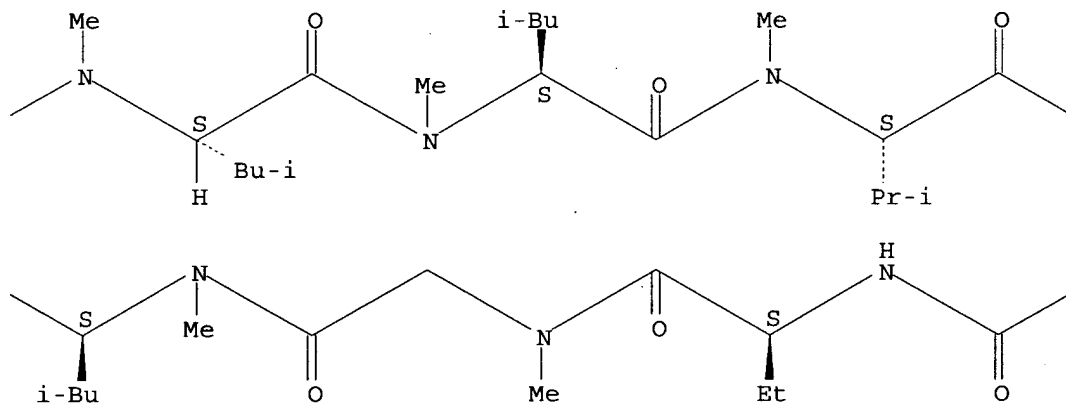
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

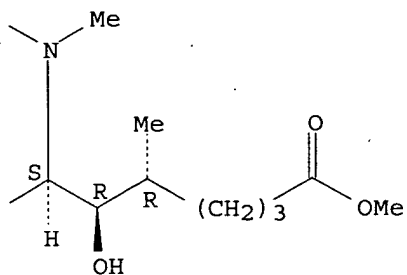
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

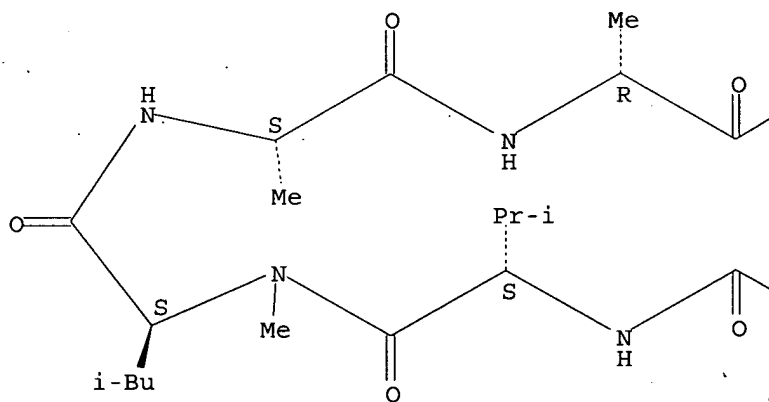




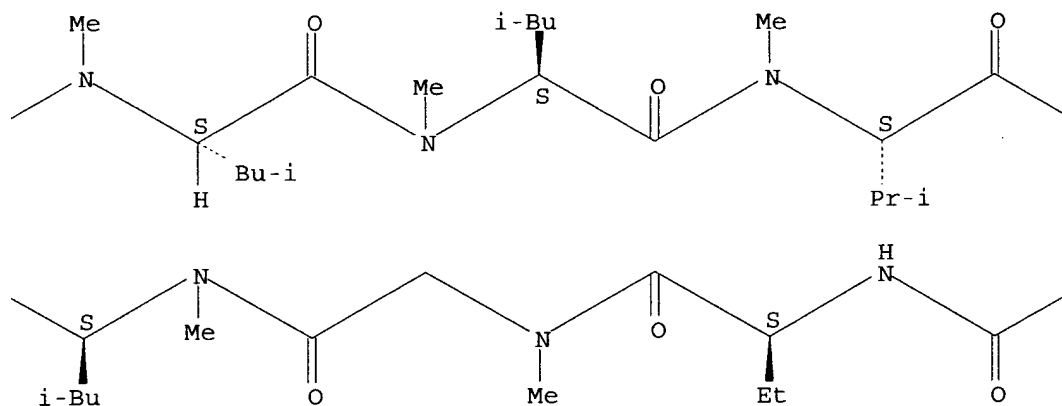
RN 502998-23-4 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)

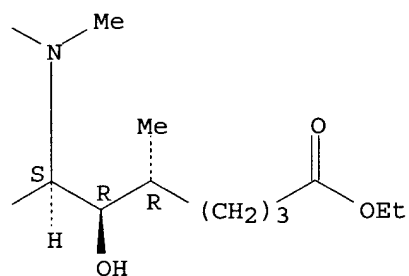
Absolute stereochemistry.



PAGE 1-B



PAGE 1-C



IT 122547-85-7 457612-98-5

RL: RCT (Reactant); RACT (Reactant or reagent)

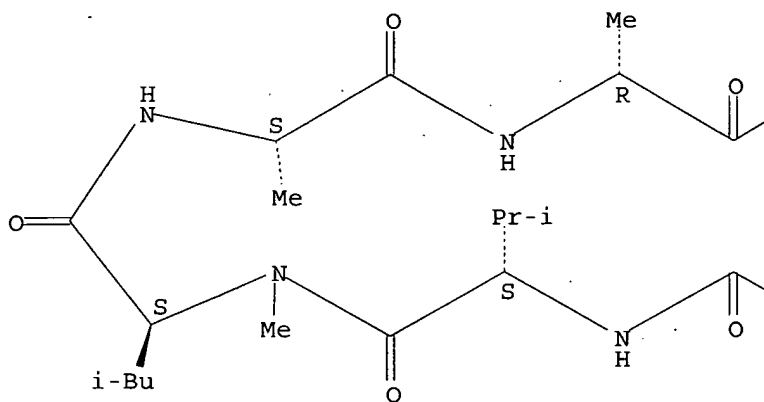
(preparation of **cyclosporin** analogs for treatment of immune disorders)

RN 122547-85-7 HCAPLUS

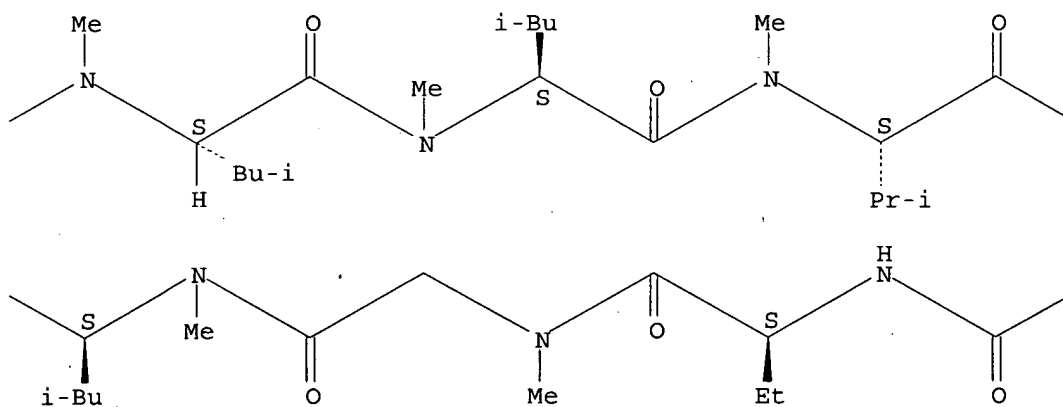
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

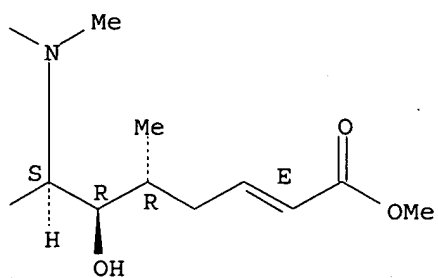
PAGE 1-A



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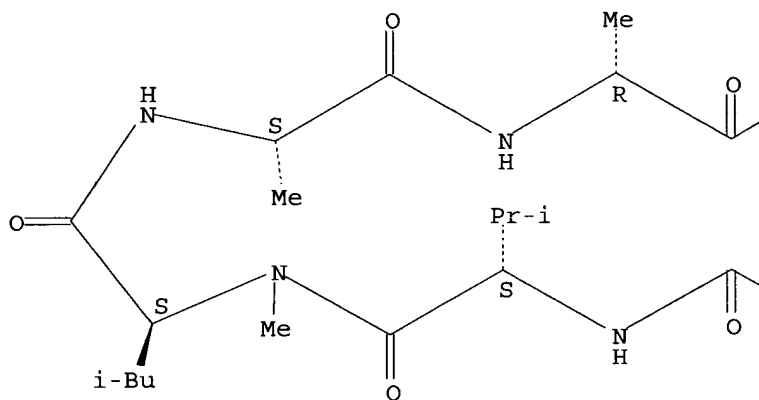


RN 457612-98-5 HCAPLUS

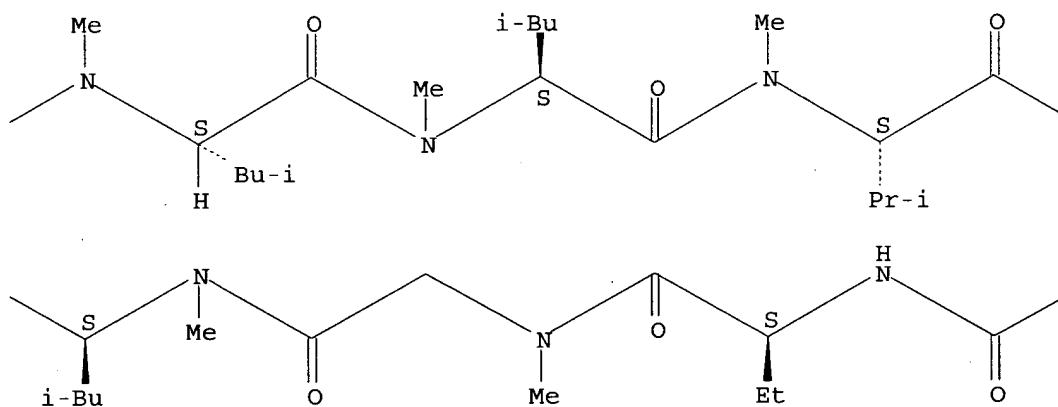
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)

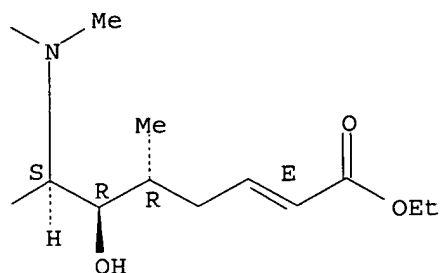
Absolute stereochemistry.
Double bond geometry as shown.

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IT 59865-13-3, Cyclosporin

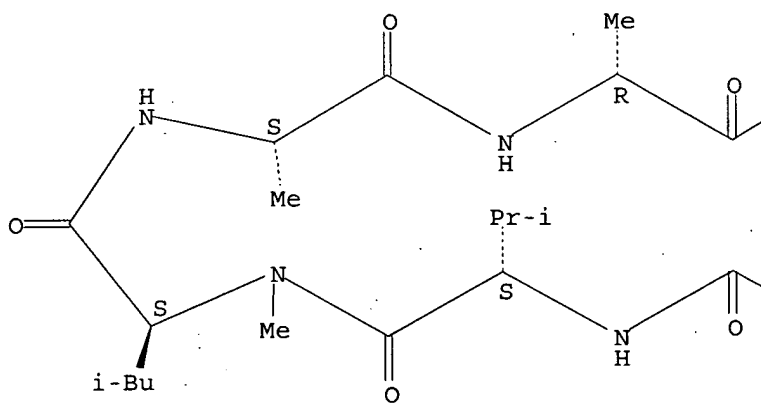
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of cyclosporin analogs for treatment of immune disorders)

RN 59865-13-3 HCAPLUS

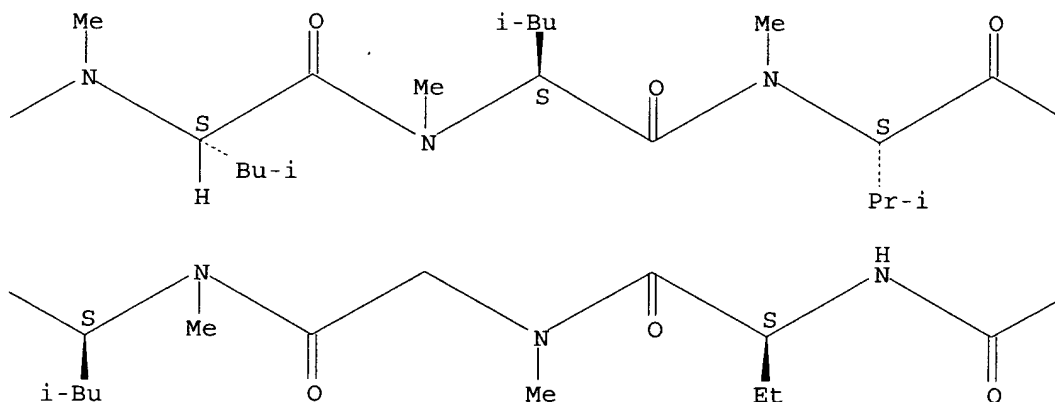
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

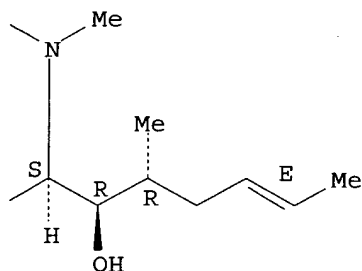
PAGE 1-A



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PAGE 1-C



L17 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:319734 HCAPLUS
 DOCUMENT NUMBER: 138:338494
 TITLE: Preparation of **cyclosporin** analogs for the treatment of autoimmune diseases
 INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Hamann, Blake; Chen, Jason
 PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 41 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033010	A1	20030424	WO 2002-US32118	20021011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
 UG, US, UZ, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003104992 A1 20030605 US 2001-976219 20011012

US 6809077 B2 20041026

EP 1434594 A1 20040707 EP 2002-789179 20021011

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

JP 2005507911 T2 20050324 JP 2003-535812 20021011

PRIORITY APPLN. INFO.: US 2001-976219 A 20011012

WO 2002-US32118 W 20021011

OTHER SOURCE(S): CASREACT 138:338494; MARPAT 138:338494

AB The invention relates to **cyclosporin** analogs

cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeLeu-MeVal] [I; A is
 -NMeCH[CH(OH)CHMeCH₂-Z-X-Y]CO- of stereo α S, β R, γ R, where
 Z is CH:CH or CH₂CH₂, X is absent or (cyclo)alkyl, and Y is
 (un)substituted (hetero)aryl; B is - α Abu-, -Val-, -Thr- or -Nva-; U
 is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-, -[O-acyl-D-Ser]- or
 -[O-(2-acyloxyethyl)-D-Ser]- and their prodrugs or pharmaceutically-
 acceptable salts for the treatment of autoimmune diseases or the
 prevention of organ transplantation rejection. The synthesis of analogs I
 involves modification of residue -NMeCH[CH(OH)CHMeCH₂CH:CHMe]CO- (A', same
 stereo) by reaction with CH₂:CH-X-Y and optional catalytic hydrogenation.
 Thus, I (Z is CH:CH, X is absent, Y is Ph, B is - α Abu-, and U is
 -D-Ala-) was prepared by reaction of **cyclosporin** A with styrene
 using Nolan catalyst in CH₂Cl₂.

IT 121584-43-8P 126374-37-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); RACT (Reactant or reagent); USES (Uses)

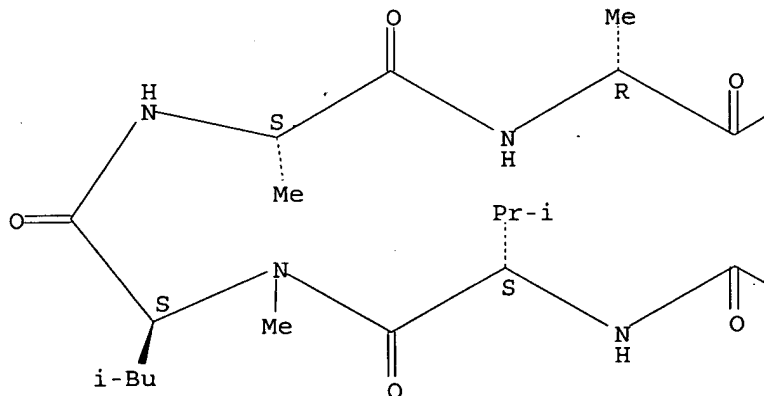
(preparation of **cyclosporin** analogs for treatment of autoimmune
 diseases)

RN 121584-43-8 HCAPLUS

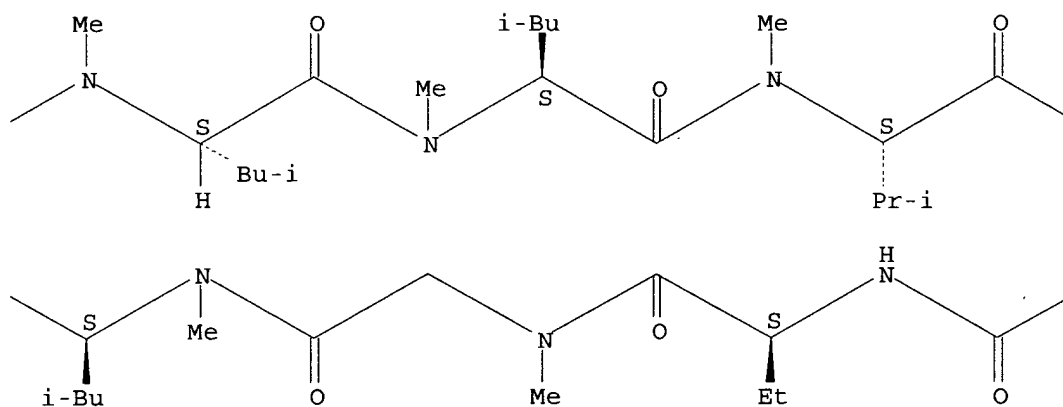
CN Cyclosporin A, 6-[(α S, β R, γ R)- β -hydroxy- γ -
 methyl- α -(methylamino)benzeneheptanoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

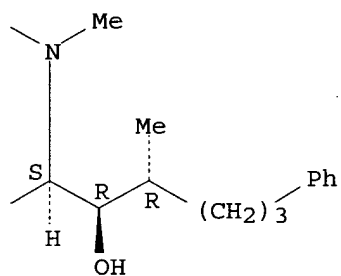
PAGE 1-A



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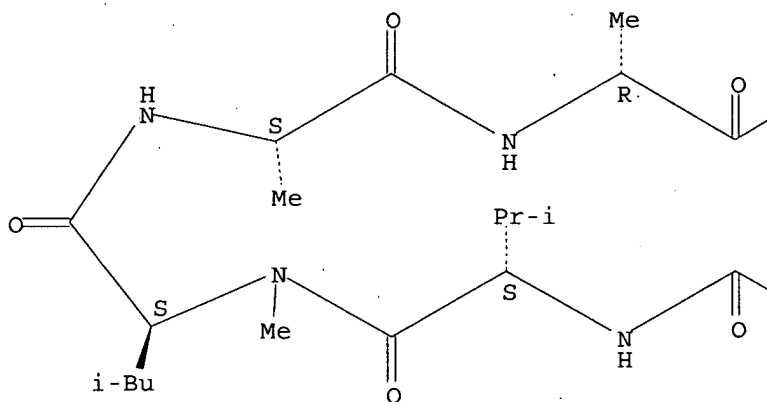


RN 126374-37-6 HCAPLUS

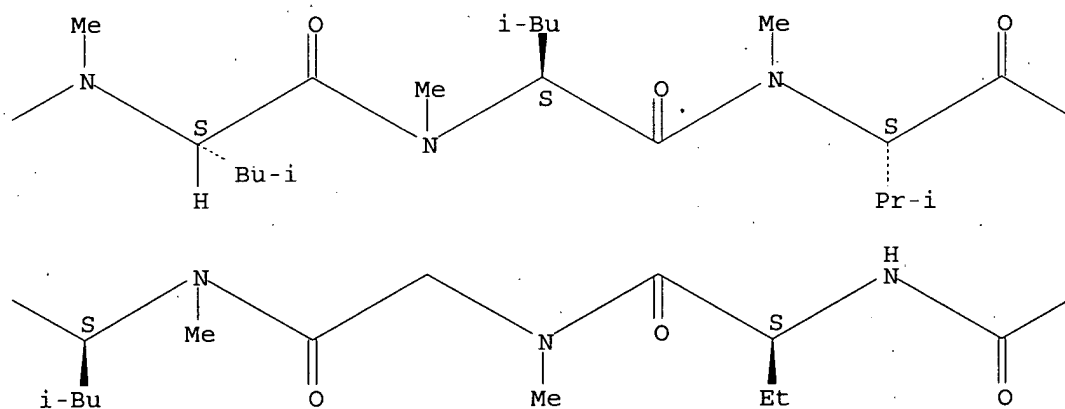
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-phenyl-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

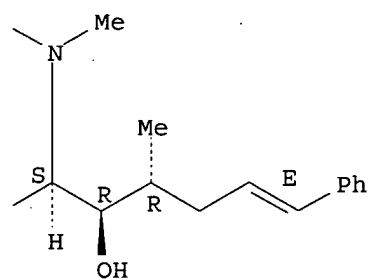
PAGE 1-A



PAGE 1-B



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IT 59865-13-3DP, Cyclosporin, analogs 515159-30-5P

515159-31-6P 515159-32-7P 515159-33-8P
 515159-34-9P 515159-35-0P 515159-36-1P
 515159-37-2P 515159-38-3P 515159-39-4P
 515159-40-7P 515159-41-8P 515159-42-9P
 515159-43-0P 515159-44-1P 515159-45-2P
 515159-46-3P 515159-47-4P 515159-48-5P
 515159-49-6P 515159-50-9P 515159-51-0P
 515159-52-1P 515159-53-2P 515159-54-3P
 515159-55-4P 515159-56-5P 515159-57-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

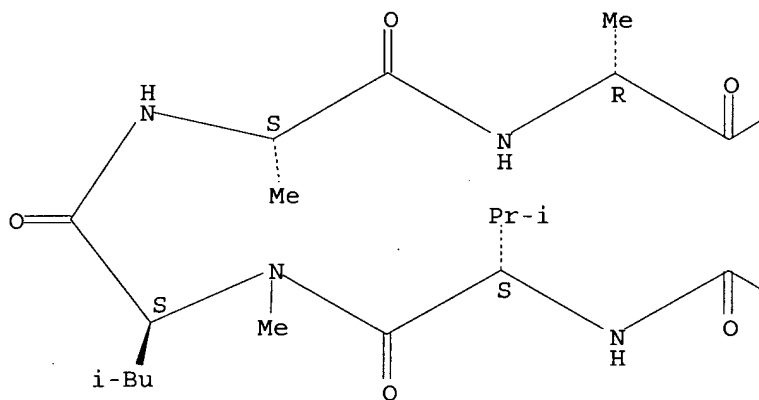
(preparation of **cyclosporin** analogs for treatment of autoimmune diseases)

RN 59865-13-3 HCAPLUS

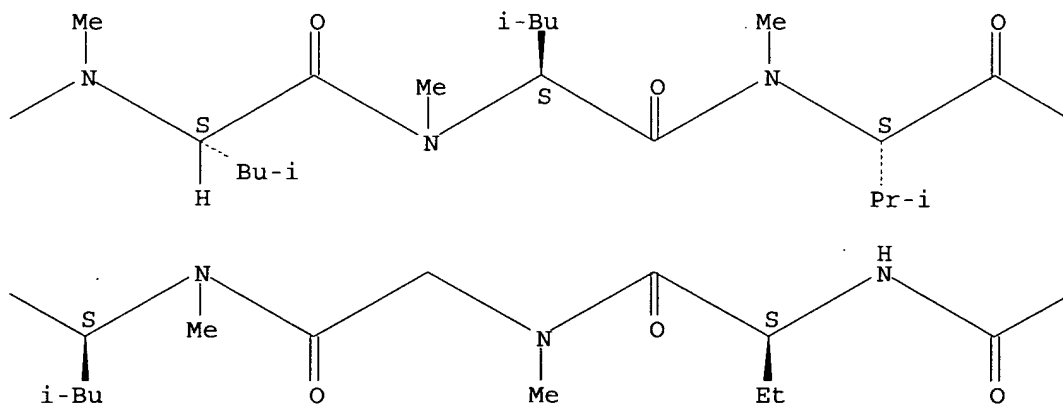
CN Cyclosporin A (9CI) (CA INDEX NAME)

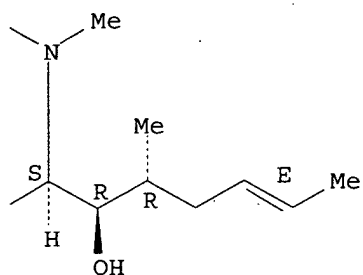
Absolute stereochemistry.
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

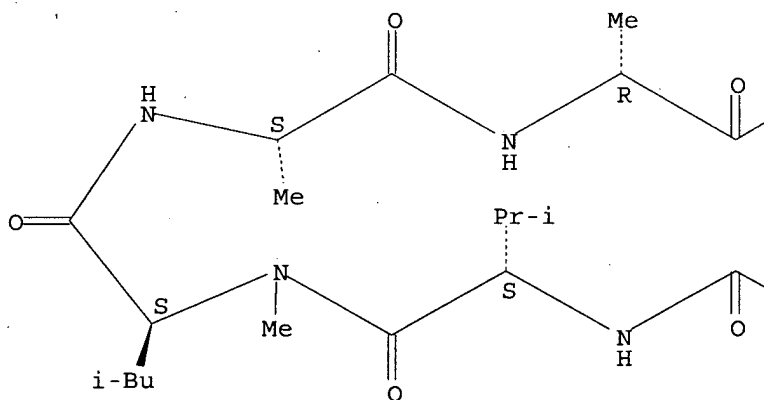




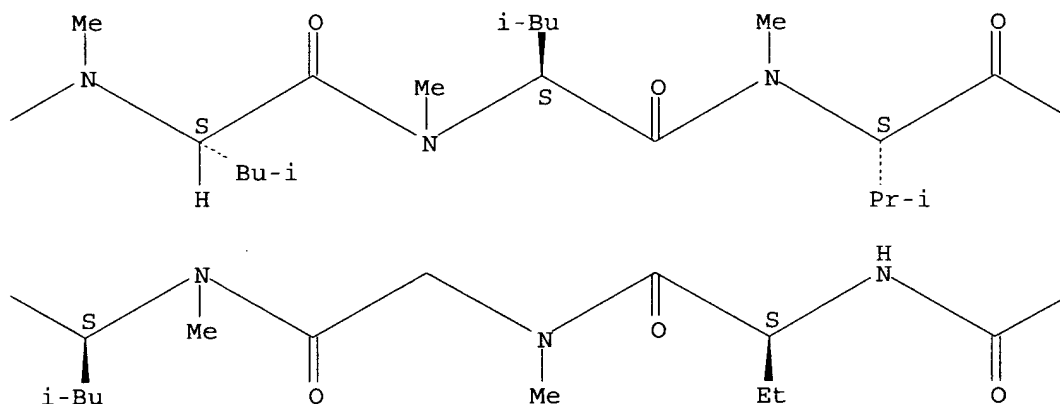
RN 515159-30-5 HCAPLUS

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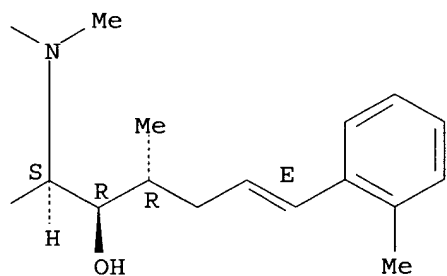
Absolute stereochemistry.
Double bond geometry as shown.



PAGE 1-B



PAGE 1-C

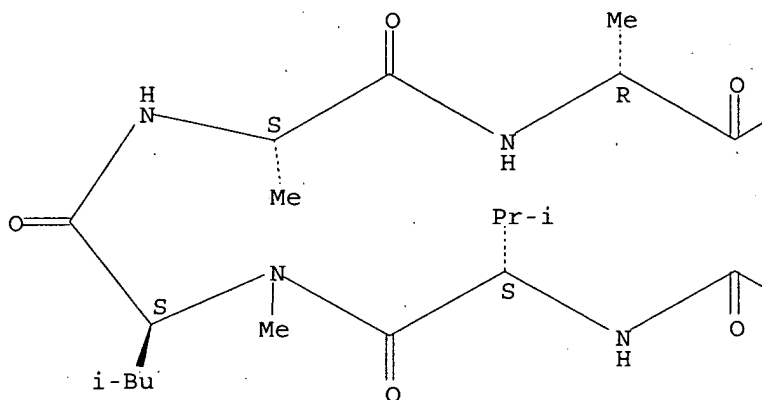


RN 515159-31-6 HCAPLUS

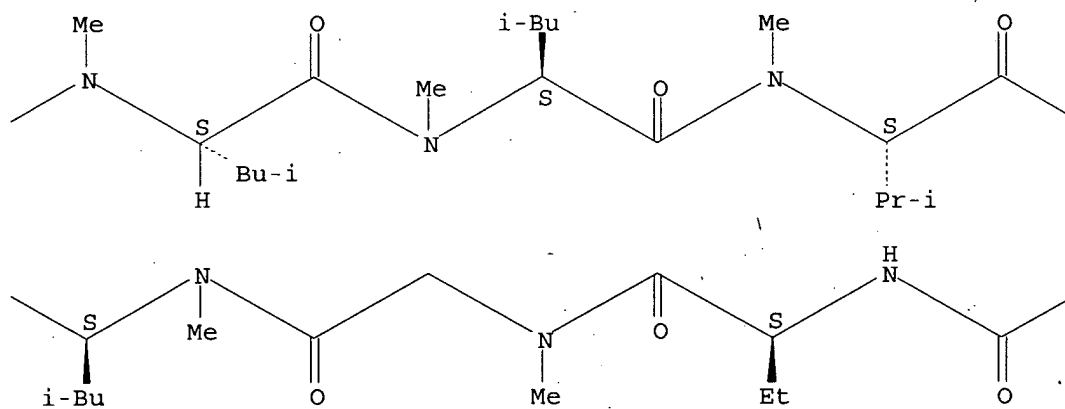
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(4-fluorophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

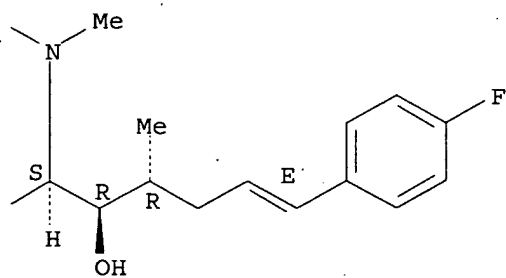
PAGE 1-A



PAGE 1-B



PAGE 1-C

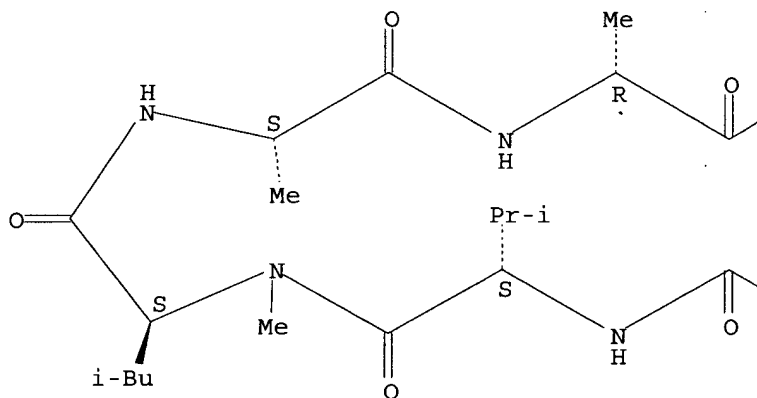


RN 515159-32-7 HCAPLUS

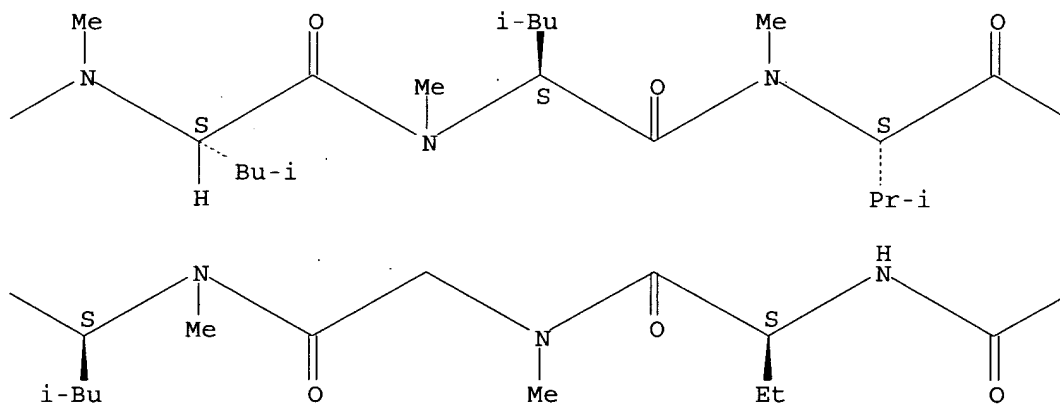
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-[4-(trifluoromethyl)phenyl]-6-heptenoic acid]- (9CI) (CA INDEX NAME)

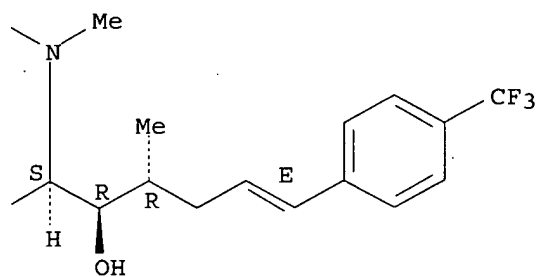
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

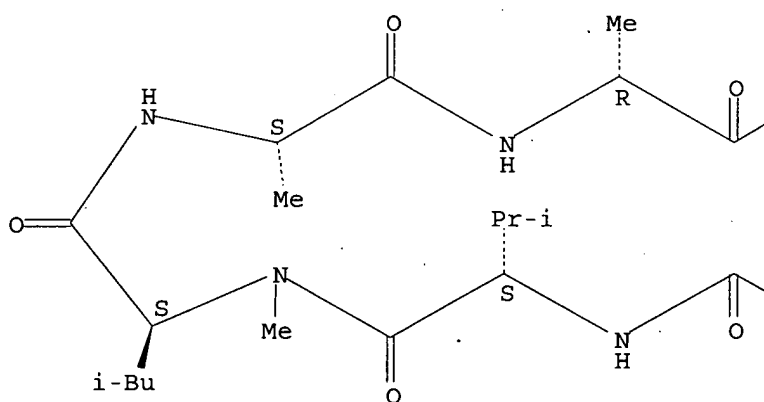




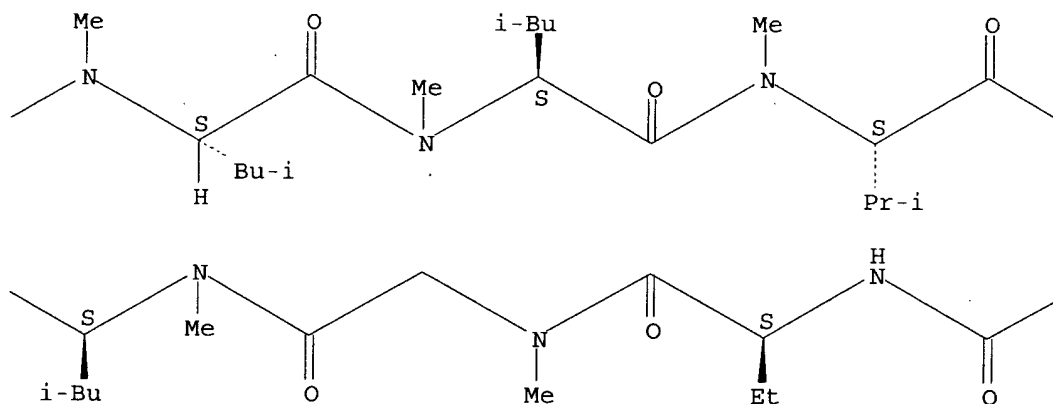
RN 515159-33-8 HCAPLUS

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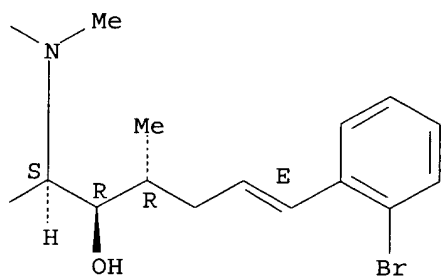
Absolute stereochemistry.
Double bond geometry as shown.



PAGE 1-B



PAGE 1-C

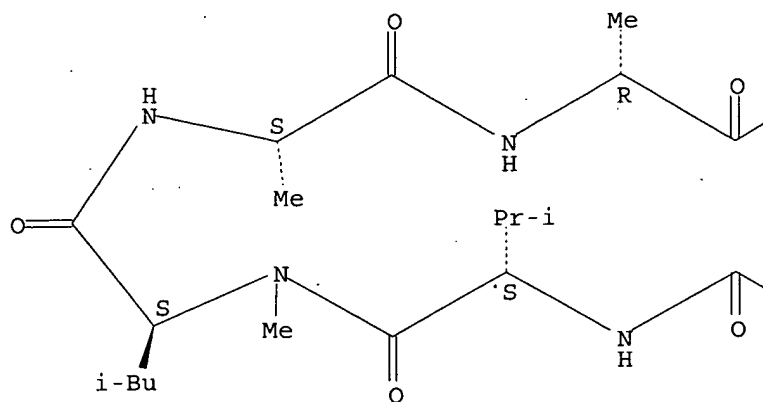


RN 515159-34-9 HCAPLUS

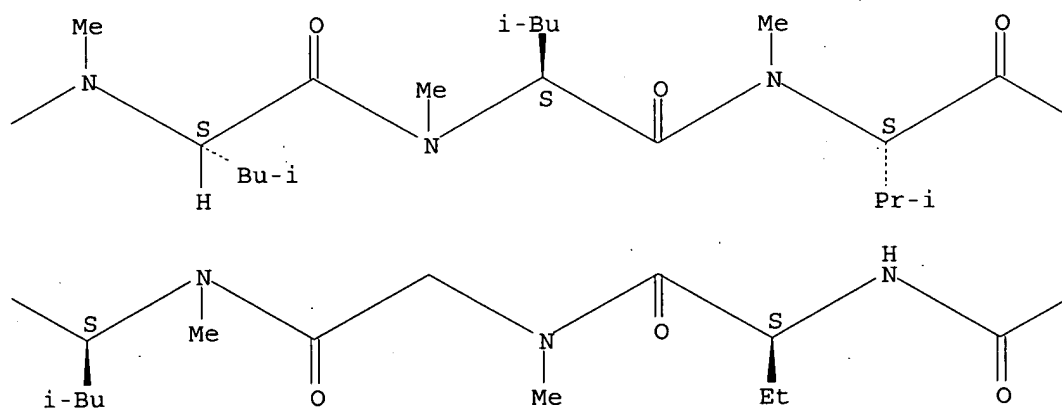
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(2-chlorophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

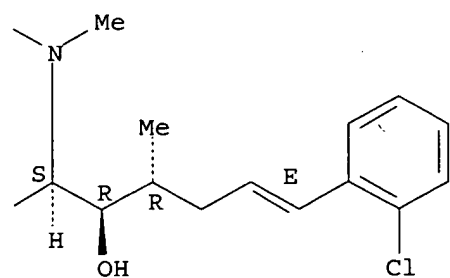
PAGE 1-A



PAGE 1-B



PAGE 1-C

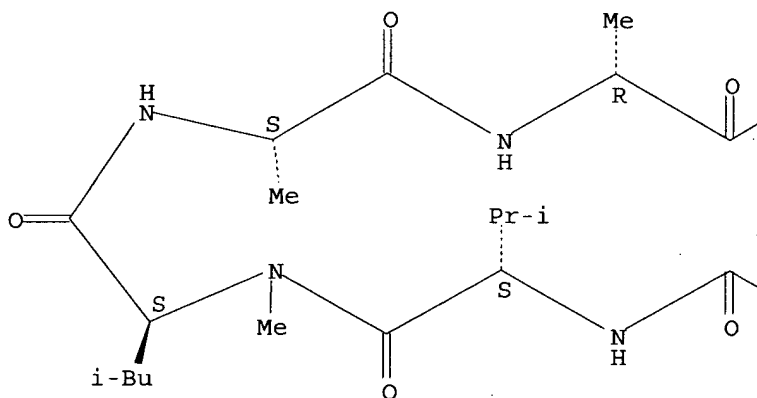


RN 515159-35-0 HCAPLUS

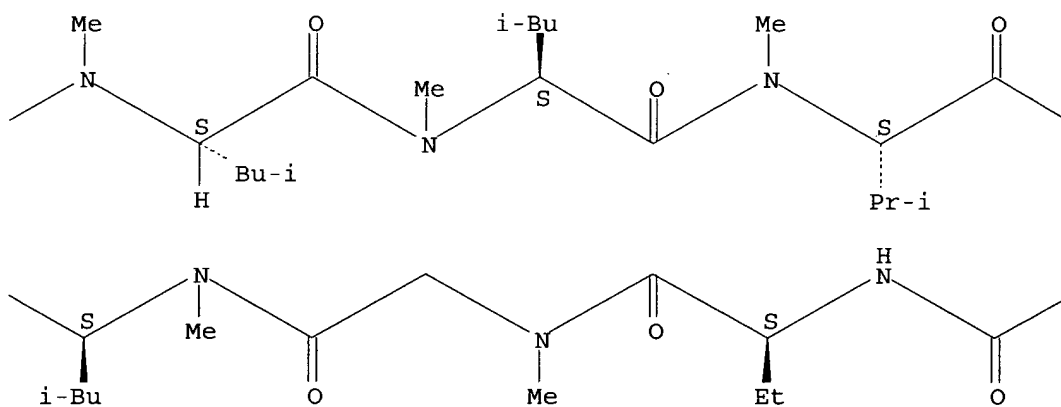
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-7-(2-methoxyphenyl)-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

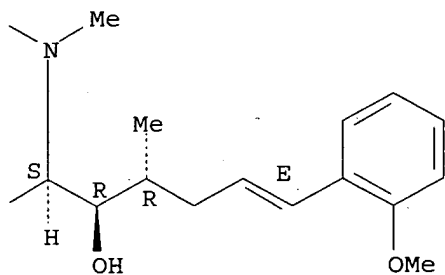
Absolute stereochemistry.
Double bond geometry as shown.

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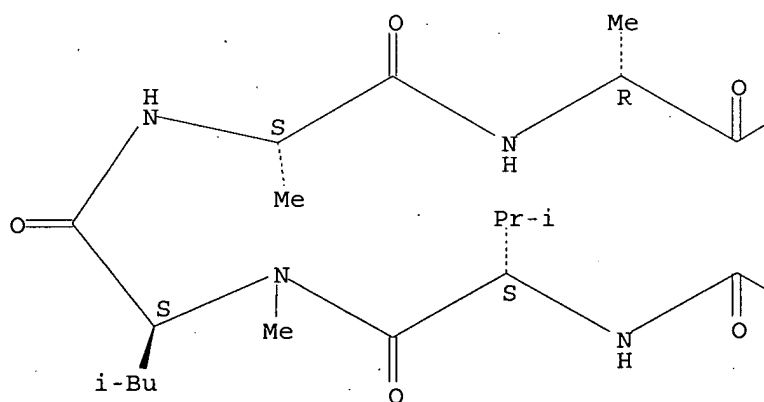




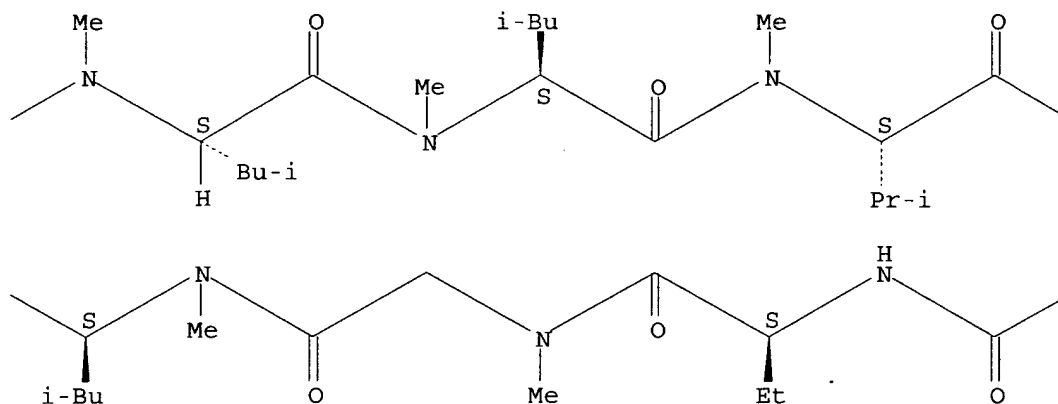
RN 515159-36-1 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(3-chlorophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

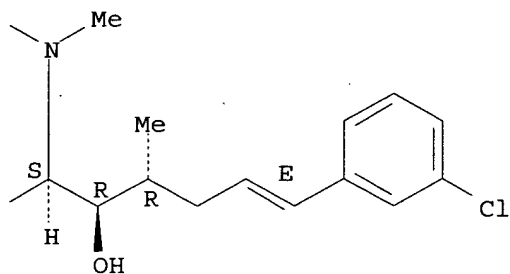
Absolute stereochemistry.
Double bond geometry as shown.



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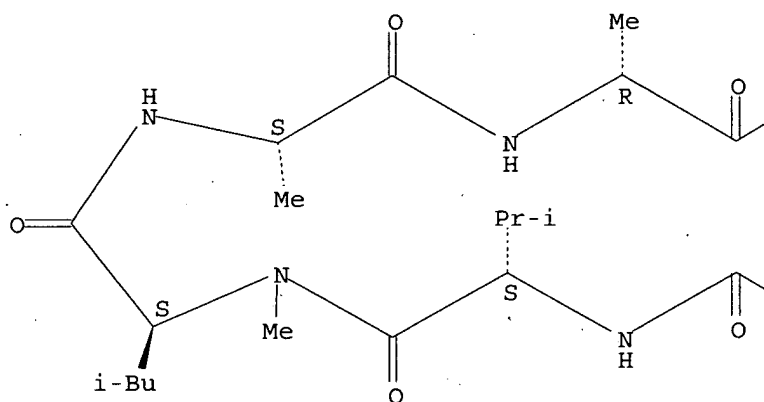


RN 515159-37-2 HCAPLUS

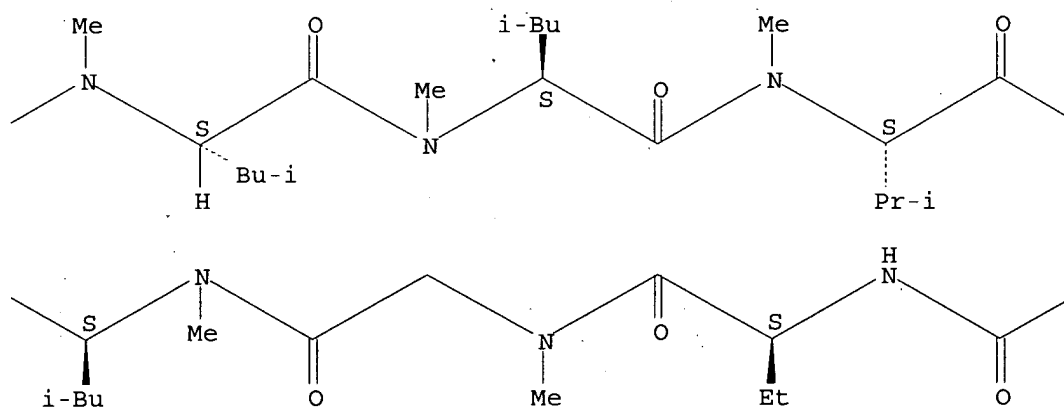
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(4-chlorophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

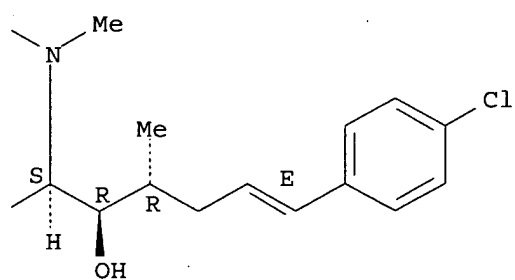
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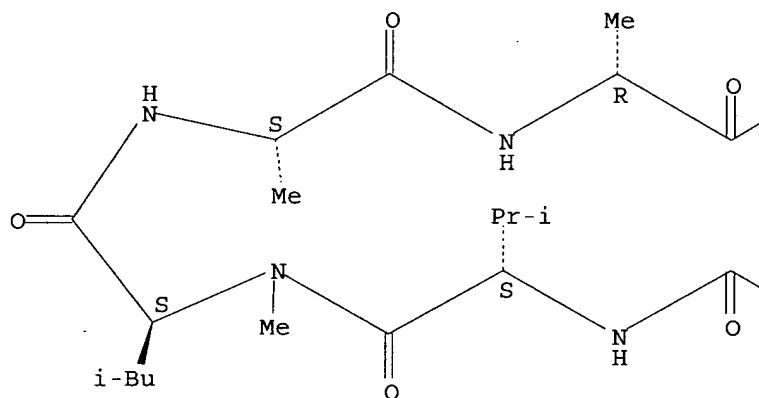


RN 515159-38-3 HCAPLUS

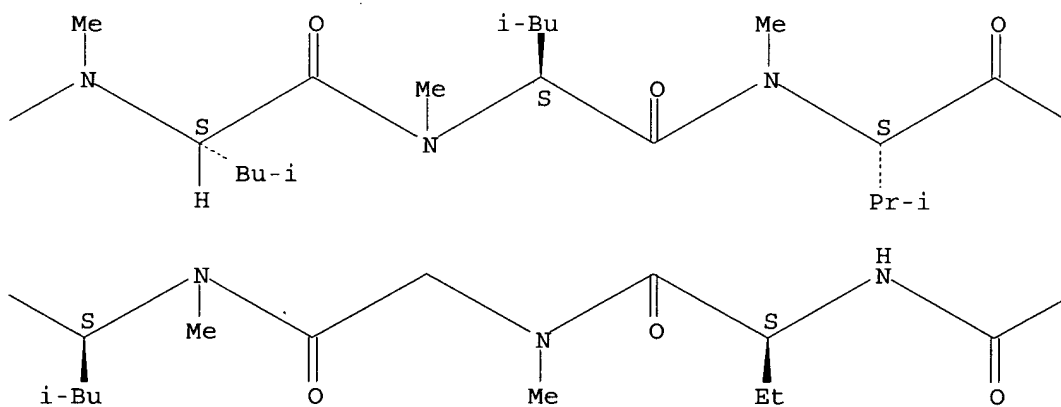
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(3-bromophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

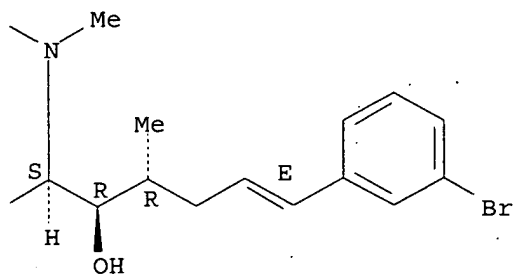
Absolute stereochemistry.
Double bond geometry as shown.

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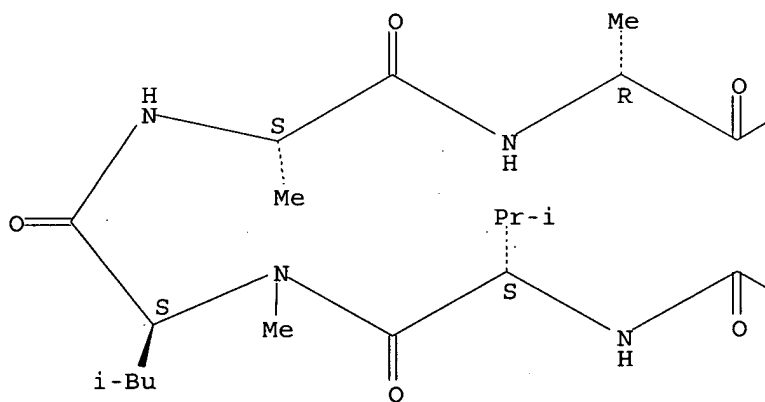




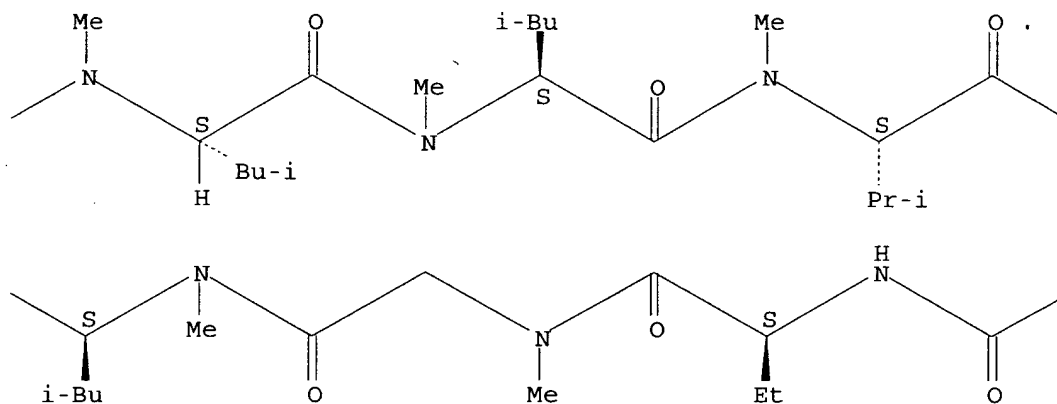
RN 515159-39-4 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(4-bromophenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

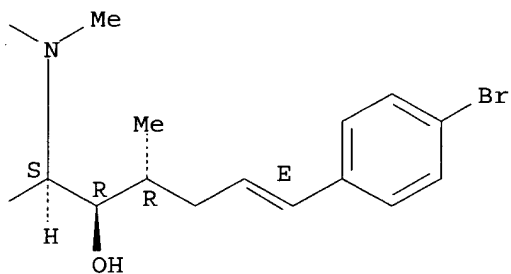
Absolute stereochemistry.
Double bond geometry as shown.



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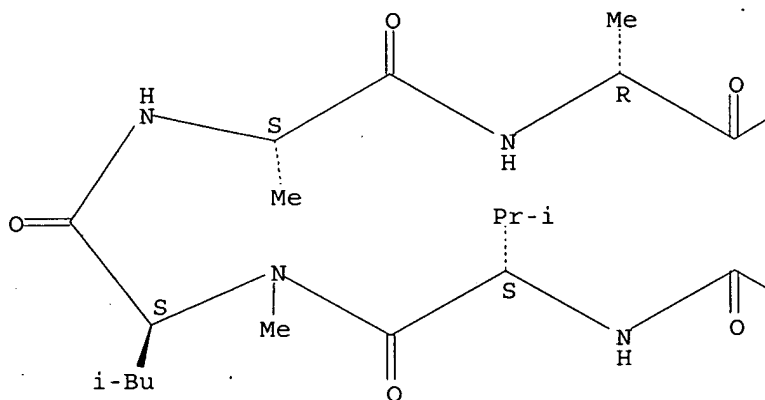


RN 515159-40-7 HCAPLUS

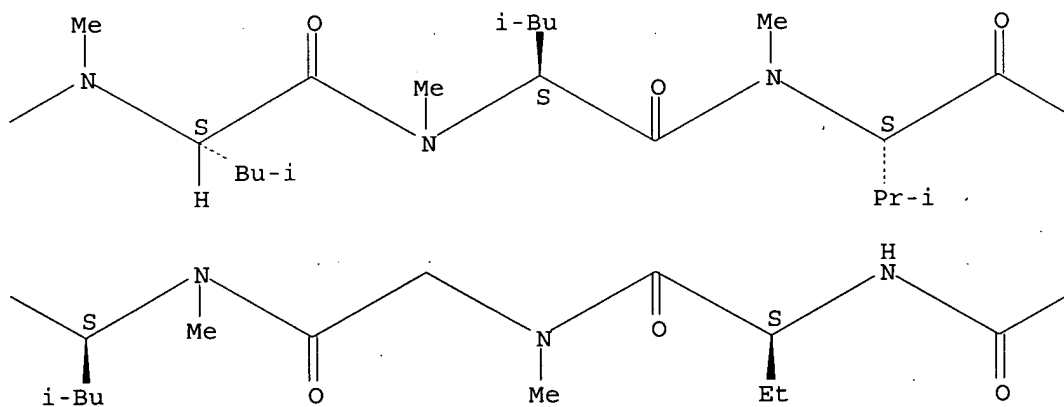
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-7-[3-(methoxycarbonyl)phenyl]-4-methyl-2-(methoxycarbonyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

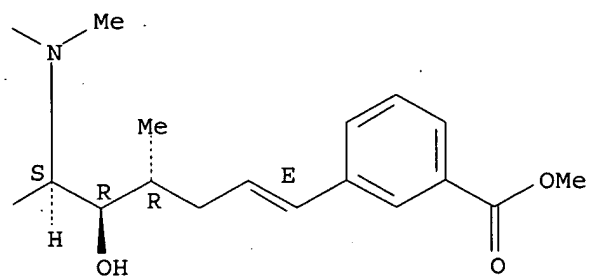
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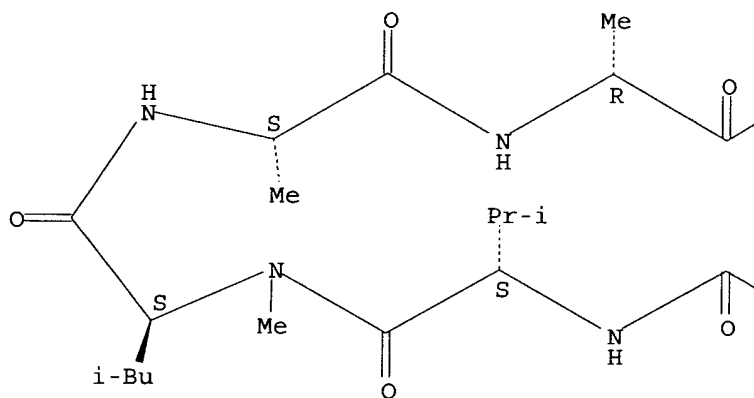


RN 515159-41-8 HCAPLUS

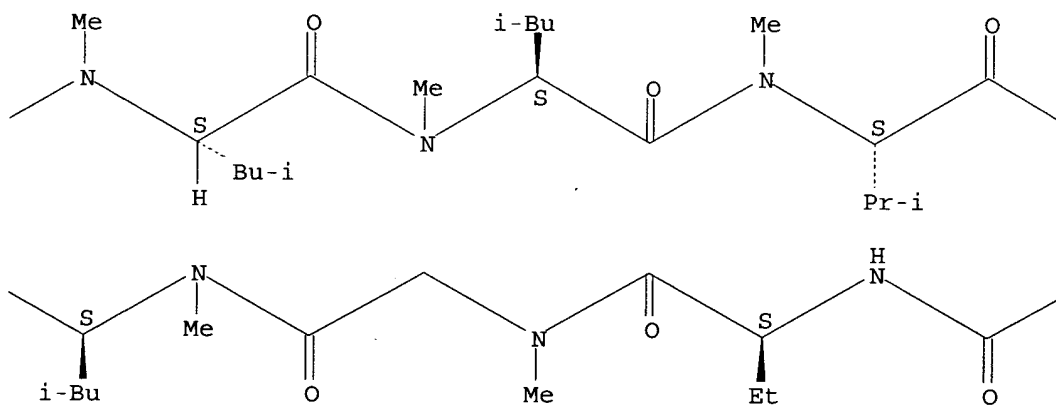
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-7-[4-(methoxycarbonyl)phenyl]-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

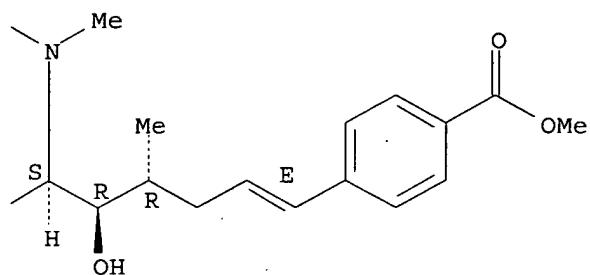
Absolute stereochemistry.
Double bond geometry as shown.

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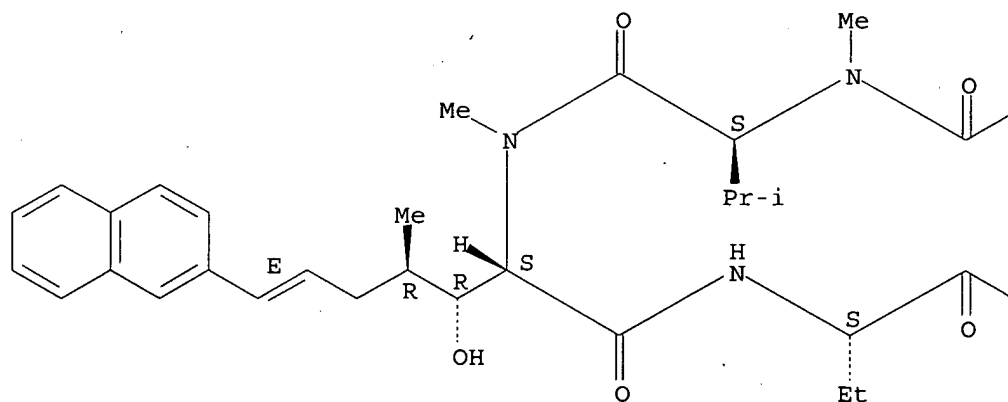




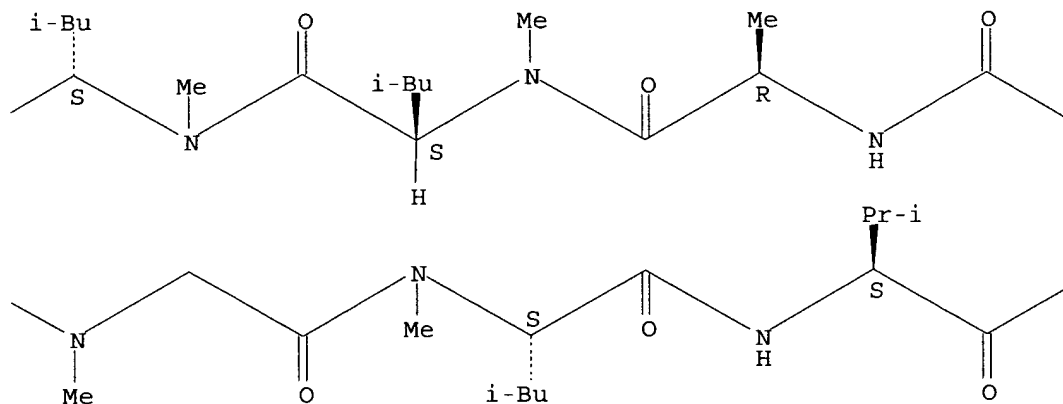
RN 515159-42-9 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(2-naphthalenyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

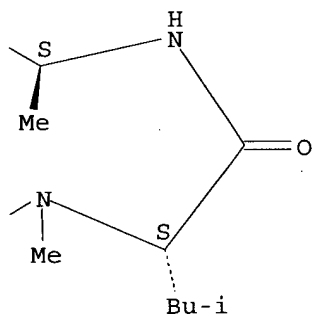
Absolute stereochemistry.
Double bond geometry as shown.



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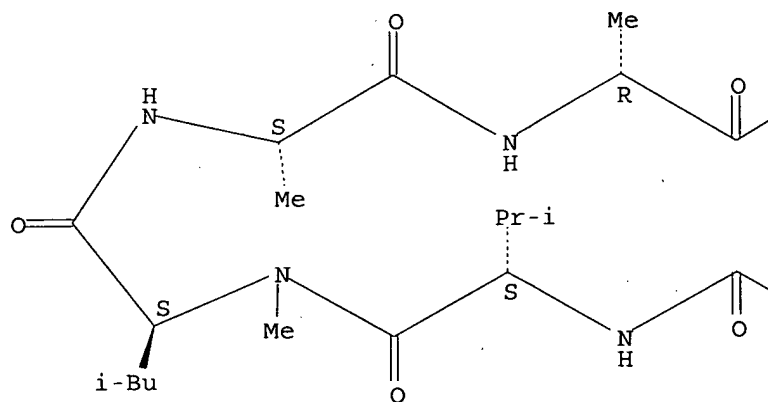


RN 515159-43-0 HCAPLUS

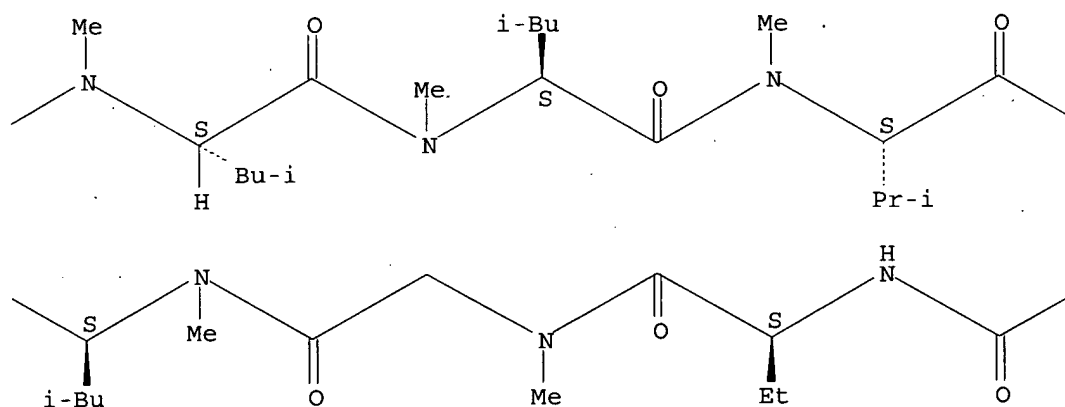
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-[4-(1,1-dimethylethyl)phenyl]-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

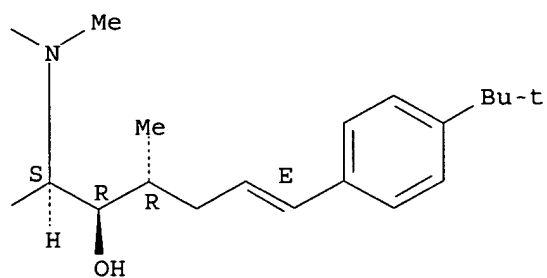
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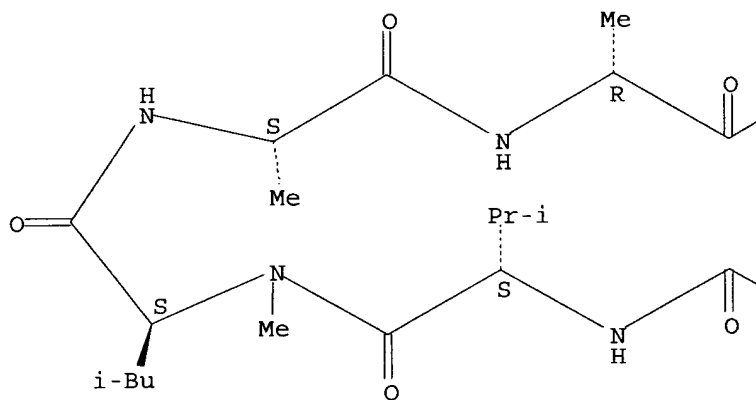


RN 515159-44-1 HCAPLUS

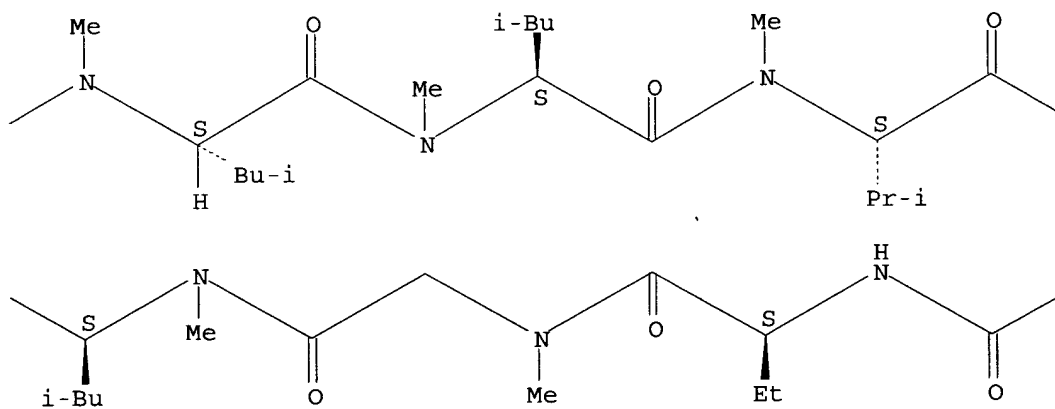
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(pentafluorophenyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

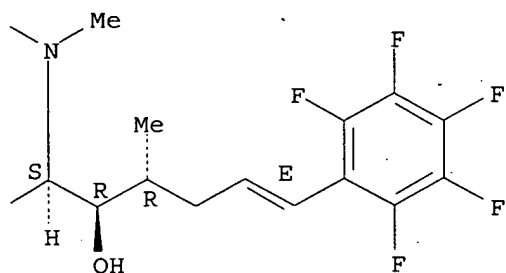
Absolute stereochemistry.
Double bond geometry as shown.

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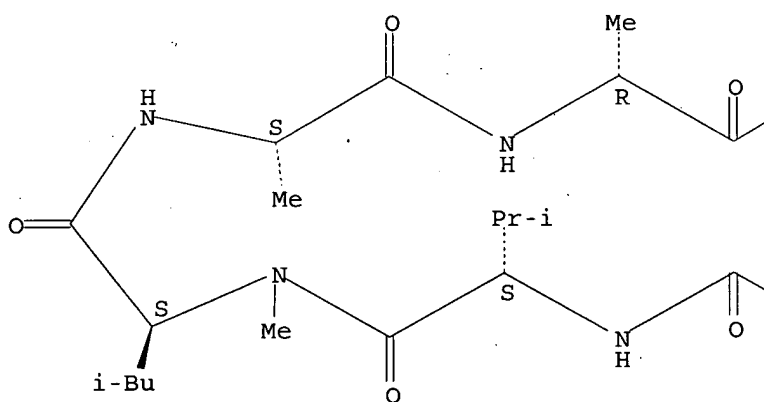




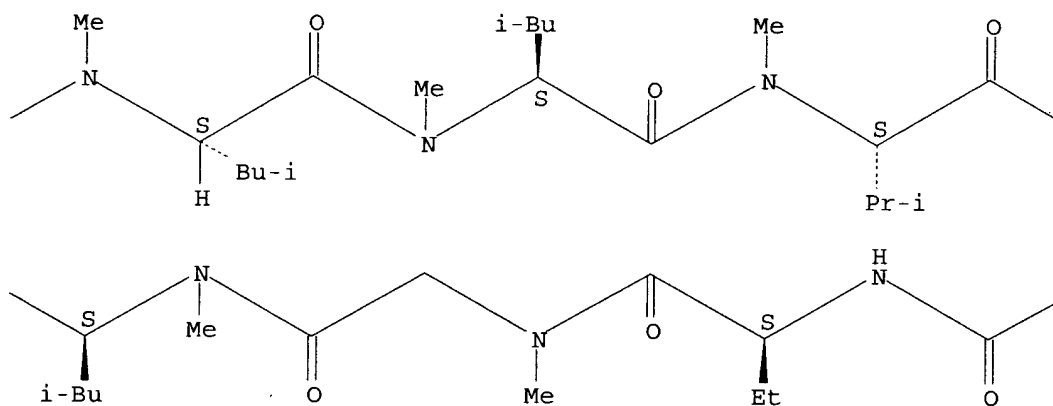
RN 515159-45-2 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-[4-(acetyloxy)phenyl]-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

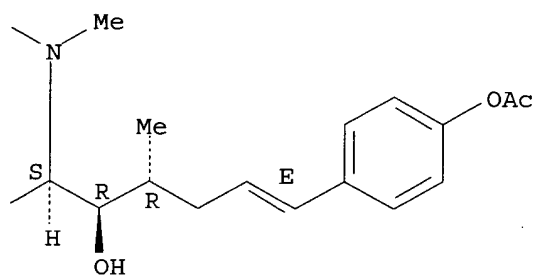
Absolute stereochemistry.
Double bond geometry as shown.



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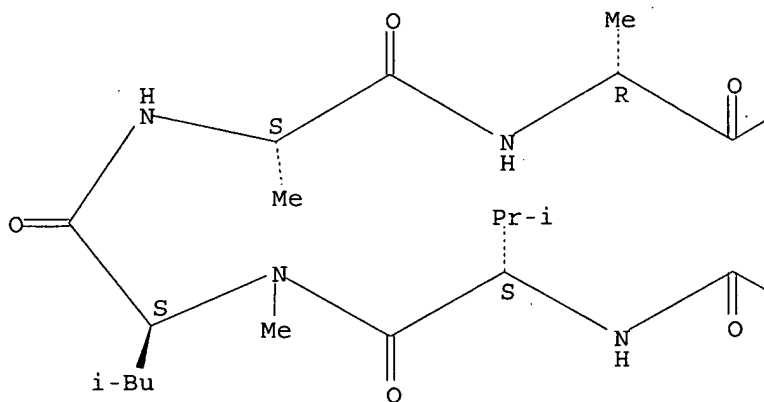


RN 515159-46-3 HCAPLUS

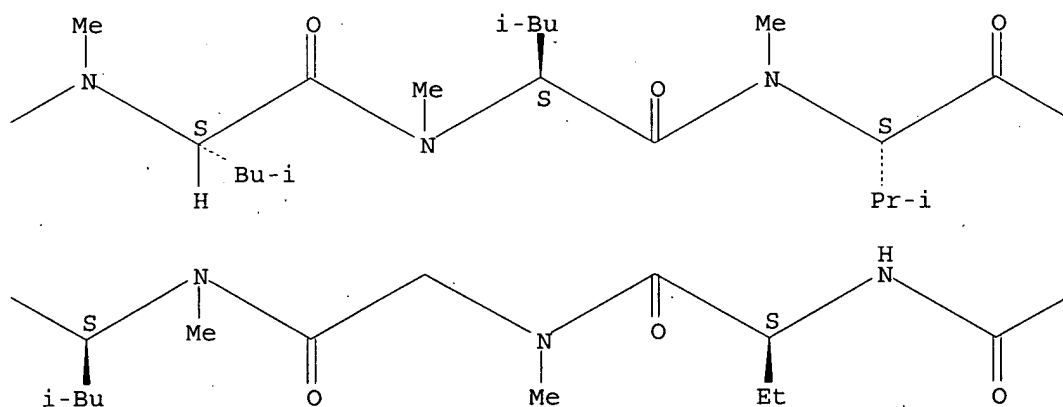
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-7-(4-methoxyphenyl)-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

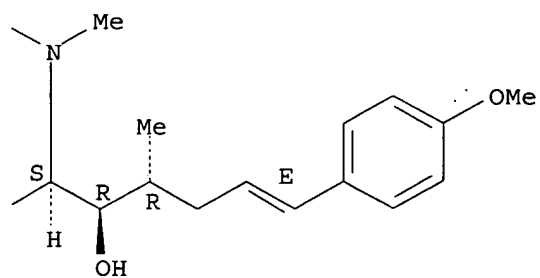
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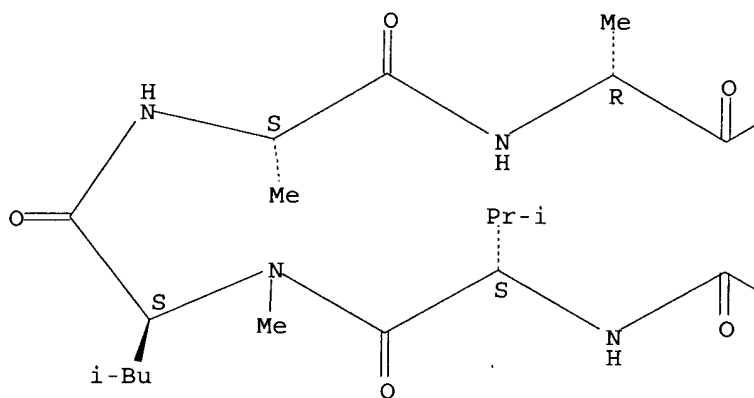


RN 515159-47-4 HCAPLUS

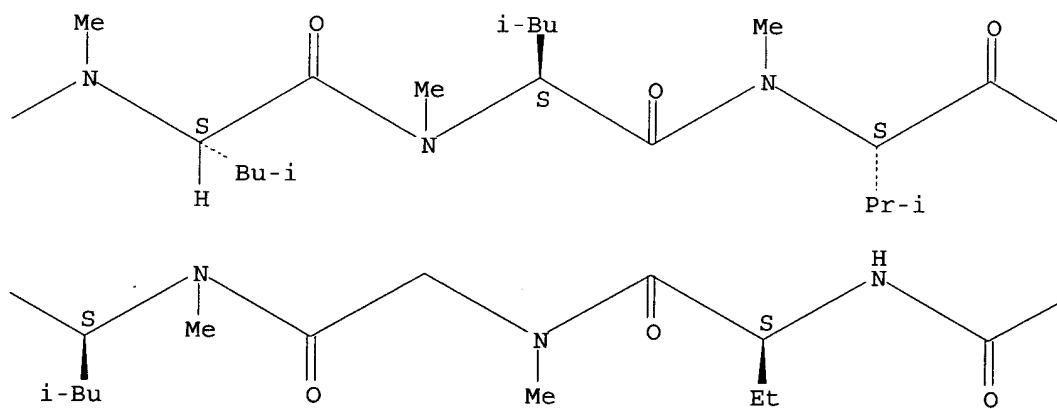
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(3,4-dimethoxyphenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

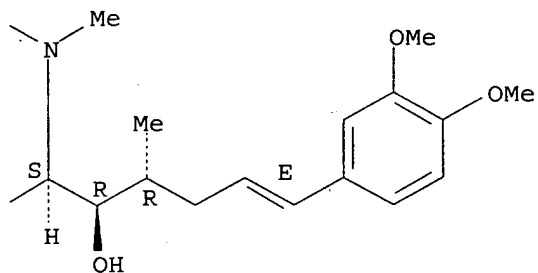
Absolute stereochemistry.
Double bond geometry as shown.

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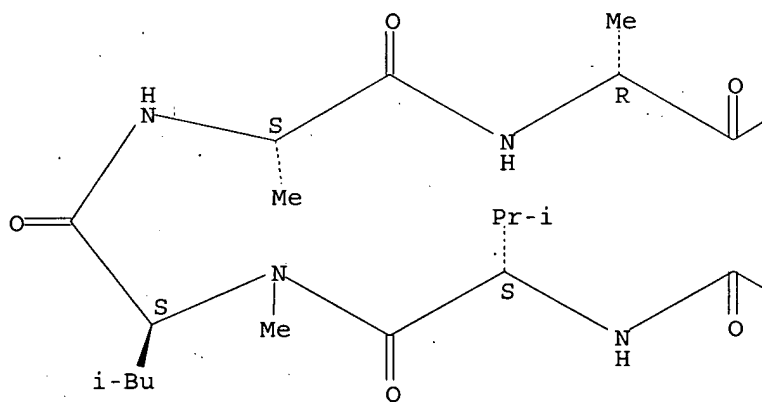




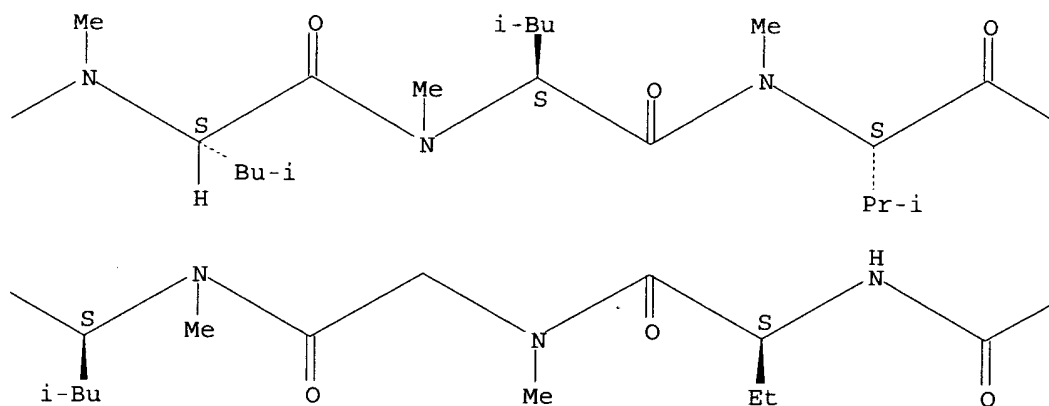
RN 515159-48-5 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-7-(2,5-dimethylphenyl)-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

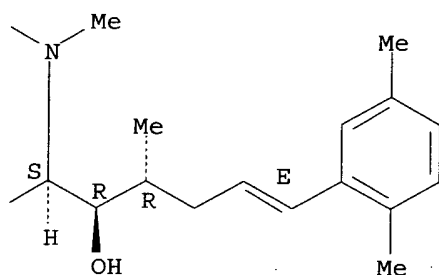
Absolute stereochemistry.
Double bond geometry as shown.



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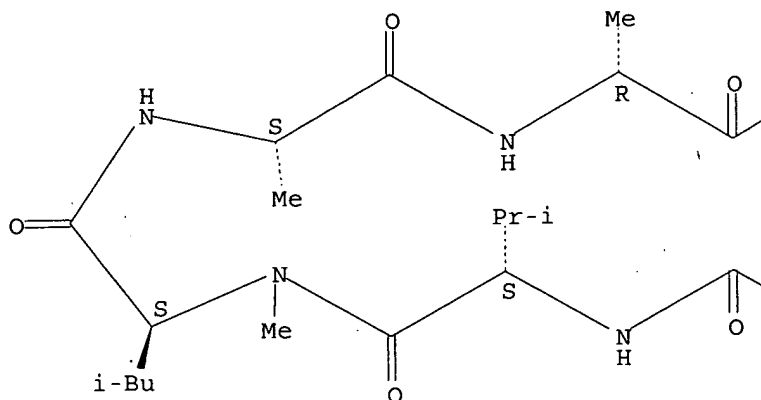
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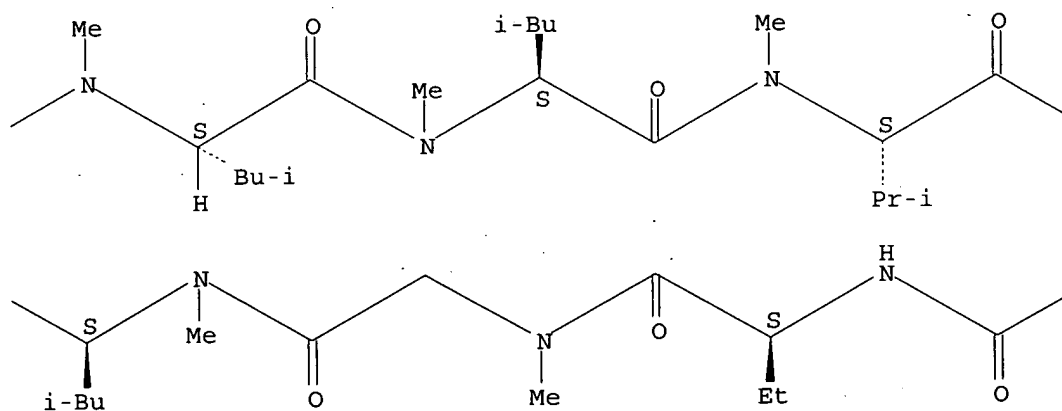
RN 515159-49-6 HCAPLUS
 CN Cyclosporin A, 6-[(α S, β R, γ R)- β -hydroxy- γ ,2-dimethyl- α -(methylamino)benzeneheptanoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

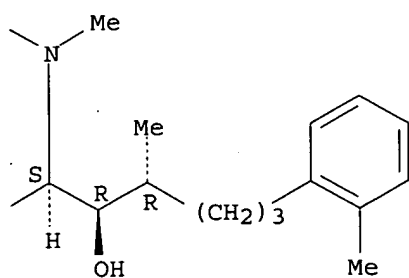
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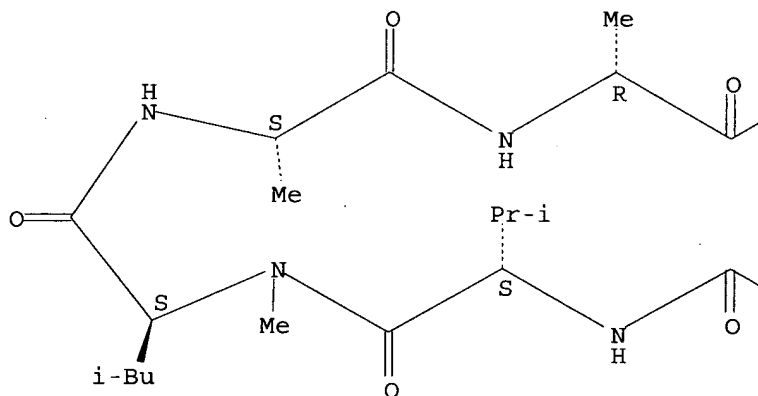


RN 515159-50-9 HCAPLUS

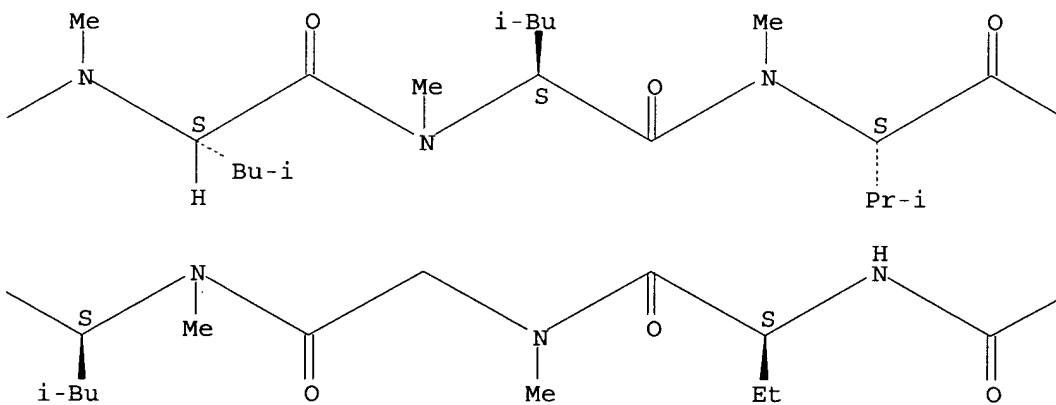
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(2-pyridinyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

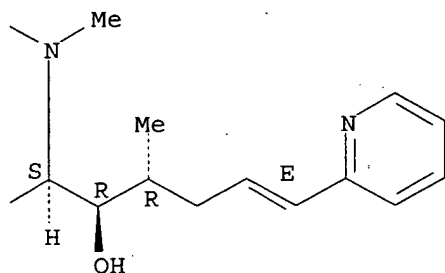
Absolute stereochemistry.
Double bond geometry as shown.

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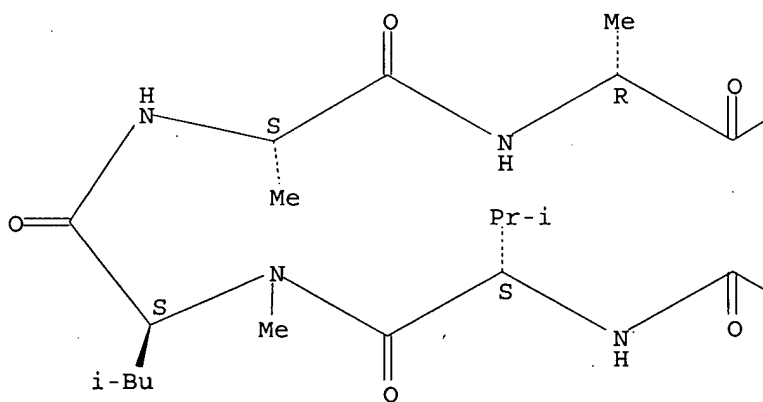




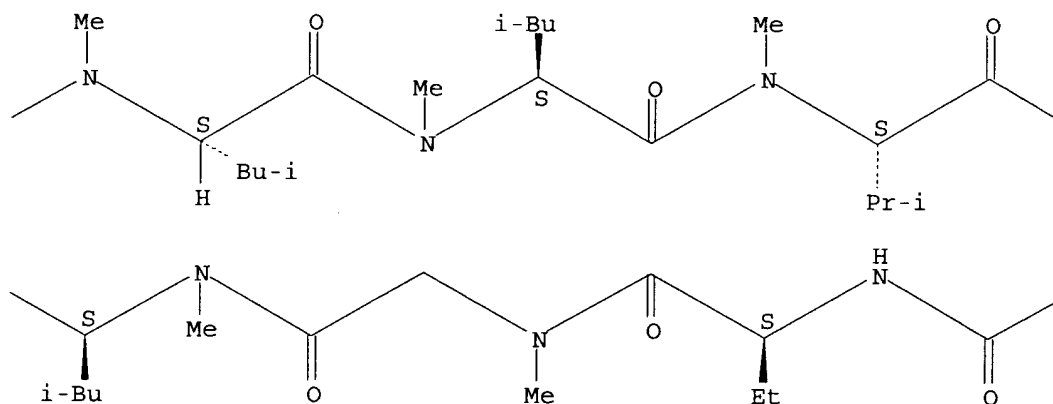
RN 515159-51-0 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(1H-pyrrol-2-yl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

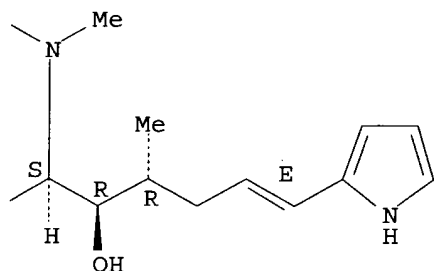
Absolute stereochemistry.
Double bond geometry as shown.



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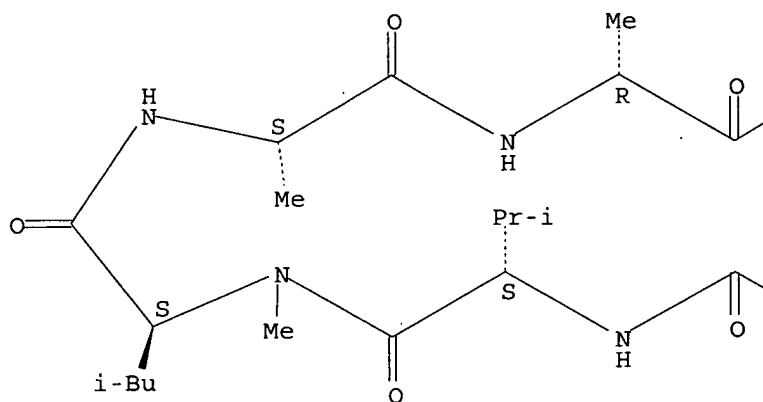


RN 515159-52-1 HCAPLUS

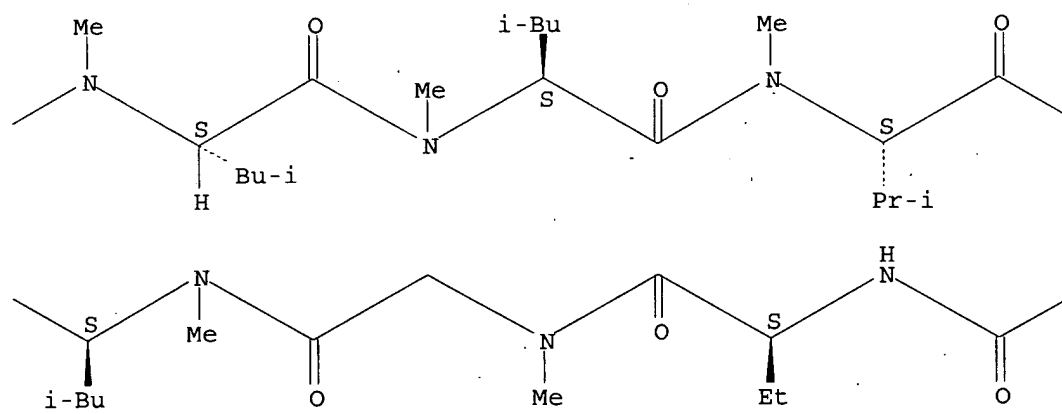
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(1-methyl-1H-pyrrol-2-yl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

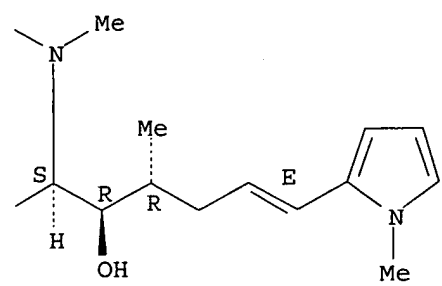
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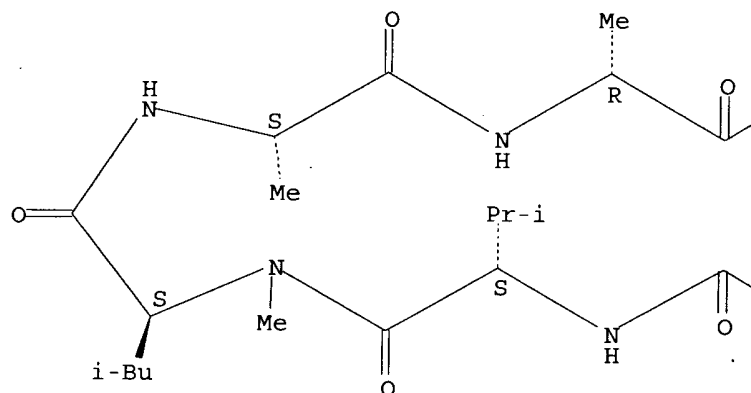


RN 515159-53-2 HCAPLUS

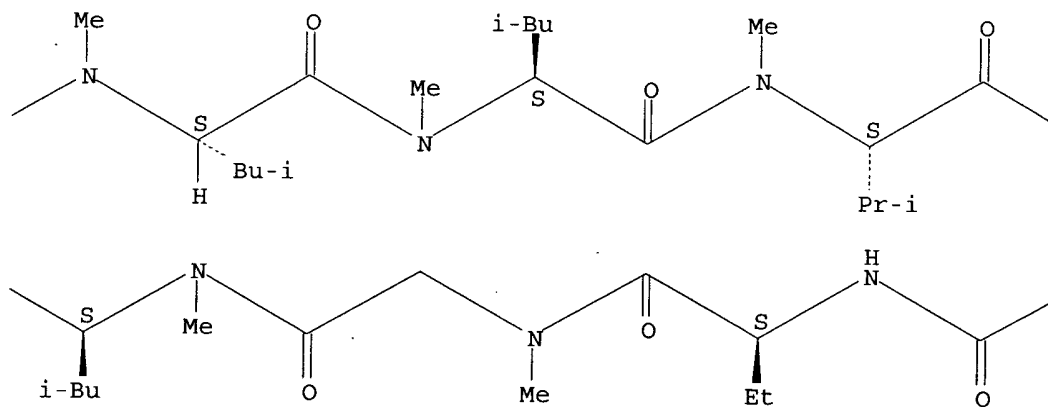
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(2-thienyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

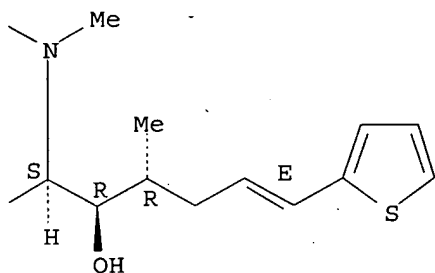
Absolute stereochemistry.
Double bond geometry as shown.

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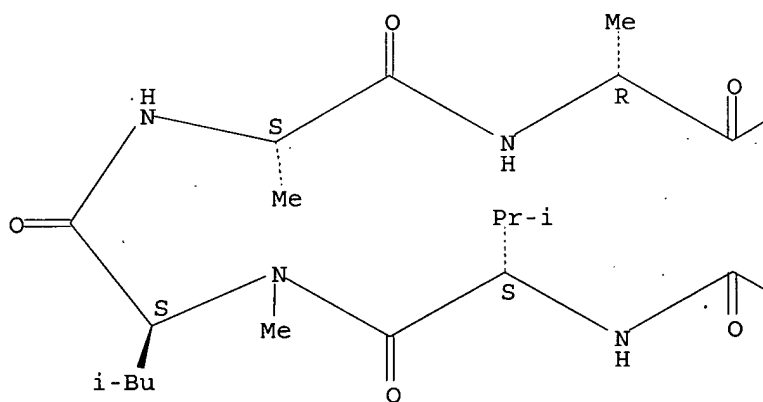




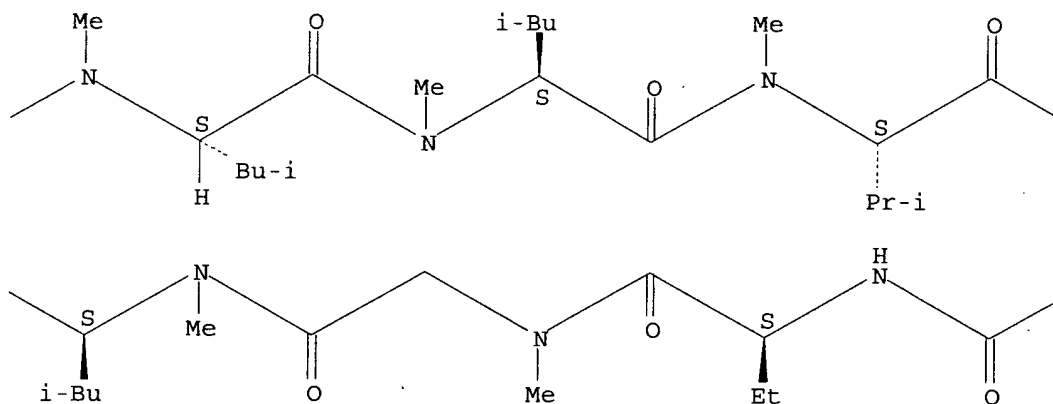
RN 515159-54-3 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(2-oxazolyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

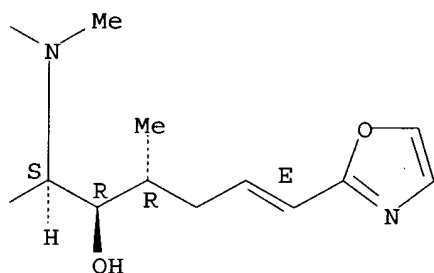
Absolute stereochemistry.
Double bond geometry as shown.



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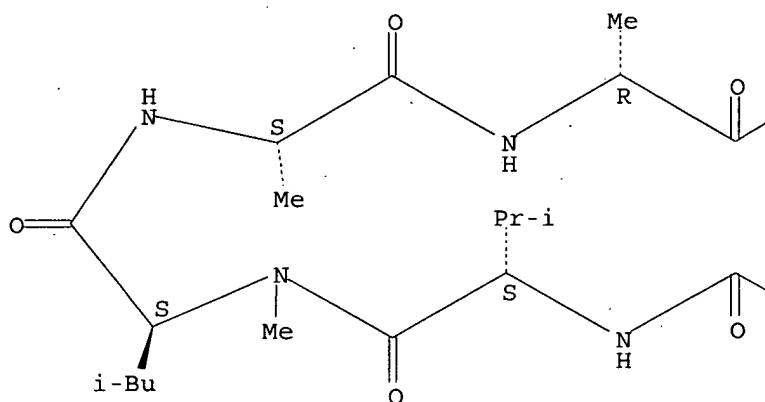


RN 515159-55-4 HCAPLUS

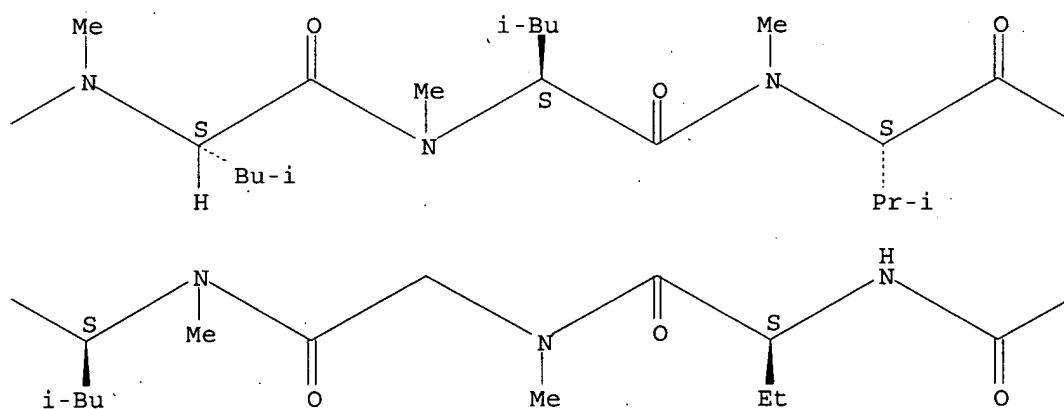
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(phenylthio)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

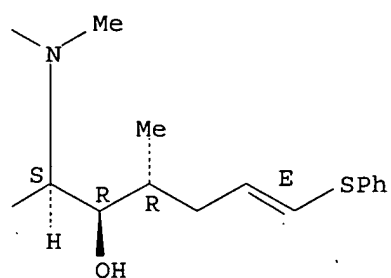
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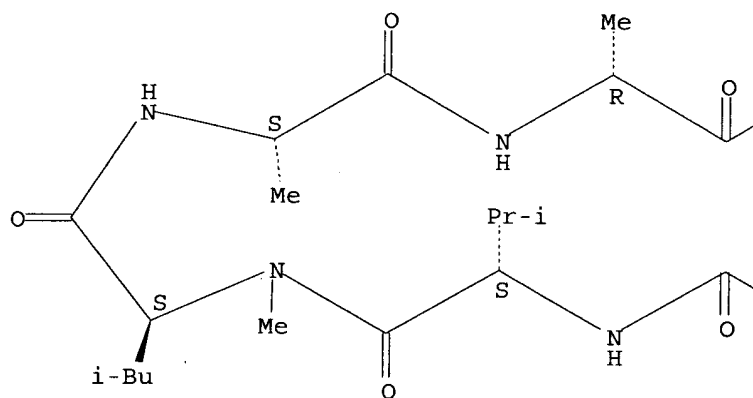


RN 515159-56-5 HCAPLUS

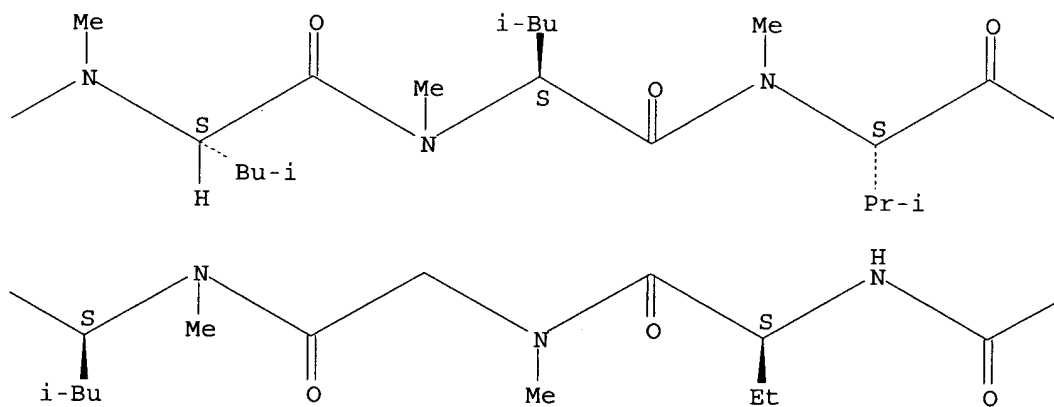
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(phenylsulfinyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

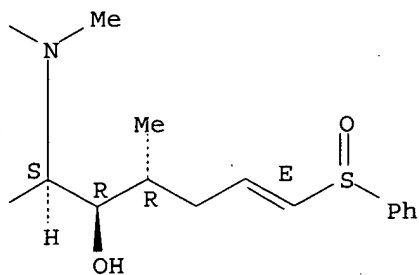
Absolute stereochemistry.
Double bond geometry as shown.

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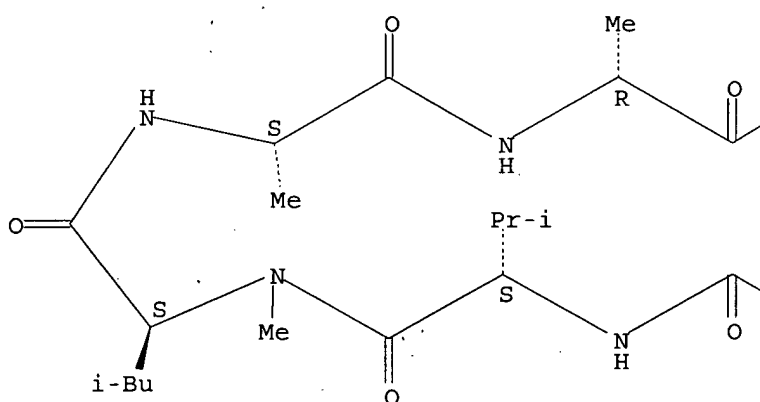




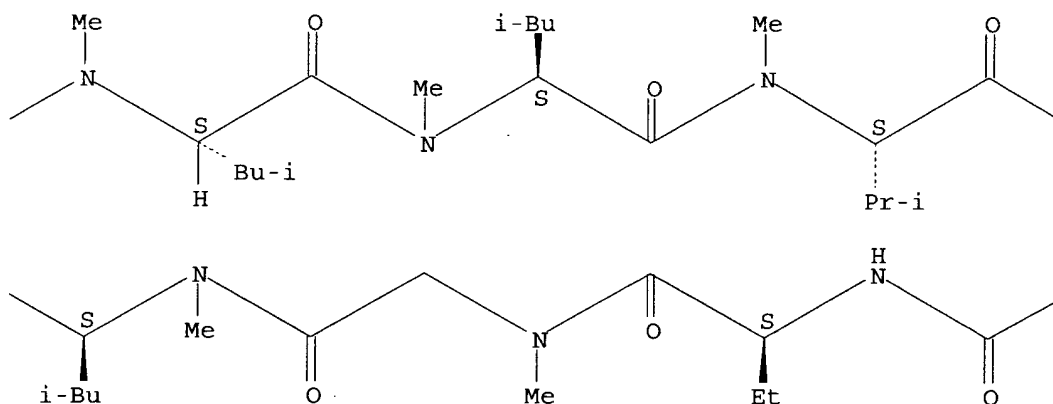
RN 515159-57-6 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-7-(phenylsulfonyl)-6-heptenoic acid]- (9CI) (CA INDEX NAME)

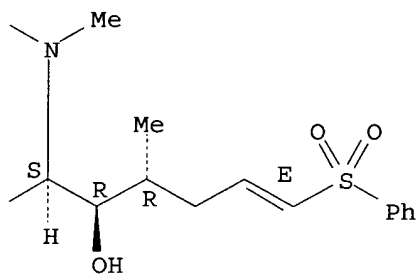
Absolute stereochemistry.
Double bond geometry as shown.



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IT 59865-13-3, Cyclosporin a

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of cyclosporin analogs for treatment of autoimmune diseases)

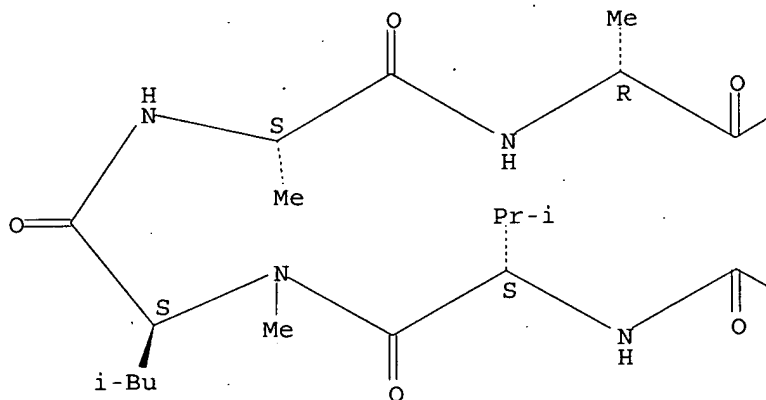
RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

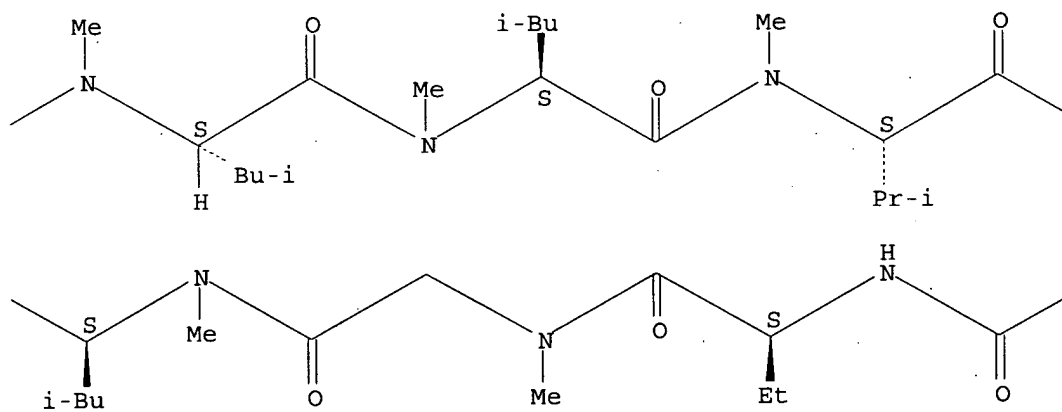
Absolute stereochemistry.

Double bond geometry as shown.

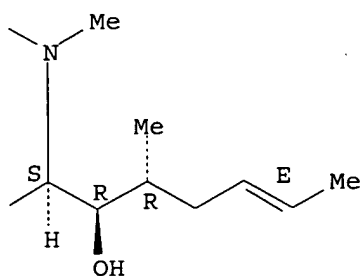
PAGE 1-A



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PAGE 1-C



REFERENCE COUNT:

4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:300843 HCAPLUS
 DOCUMENT NUMBER: 138:304531
 TITLE: Preparation of **cyclosporin** analogs for the treatment of lung diseases
 INVENTOR(S): Or, Yat Sun; Lazaroova, Tsvetelina
 PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 36 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003030834	A2	20030417	WO 2002-US32646	20021011
WO 2003030834	A3	20040415		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003087813	A1	20030508	US 2001-975923	20011012
US 2003109425	A1	20030612	US 2003-345855	20030116
PRIORITY APPLN. INFO.:			US 2001-975923	A 20011012

OTHER SOURCE(S): CASREACT 138:304531; MARPAT 138:304531

AB The invention relates to **cyclosporin** analogs
 cyclo[A-B-Sar-MeLeu-Val-MeLeu-Ala-U-MeLeu-MeVal] [I; A is -NMeCH[CH(OH)CHMe(CH₂)₃-X-Y]CO- of stereo α S, β R, γ R, where X is absent or (cyclo)alkyl and Y is (thio)carboxy or (un)substituted alkyl ester; B is - α Abu-, -Val-, -Thr- or -Nva-; U is -D-Ala-, -D-Ser-, -[O-(2-hydroxyethyl)-D-Ser]-, -[O-acyl-D-Ser]- or -[O-(2-acyloxyethyl)-D-Ser]-] and their prodrugs or pharmaceutically-acceptable salts for the treatment of asthma and related diseases. The synthesis of analogs I involves modification of residue -NMeCH[CH(OH)CHMeCH₂CH:CHMe]CO- (A', same stereo) by reaction with CH₂:CH-X-Y, followed by catalytic hydrogenation. Thus, I (X is absent, Y is CO₂Me, B is - α Abu-, and U is -D-Ala-) was prepared by hydrogenation of **cyclosporin** Me ester over Pd/C. Compds. of the invention showed IC₅₀ values 0.1 to 0.0015 μ M for inhibition of calcineurin.

IT 59865-13-3DP, **Cyclosporin**, analogs 502998-21-2P

502998-23-4P 502998-24-5P 502998-26-7P

510741-22-7P 510741-23-8P 510741-25-0P

510741-27-2P 510741-28-3P 510741-30-7P

510741-32-9P 510741-34-1P 510741-35-2P

510741-36-3P 510741-37-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

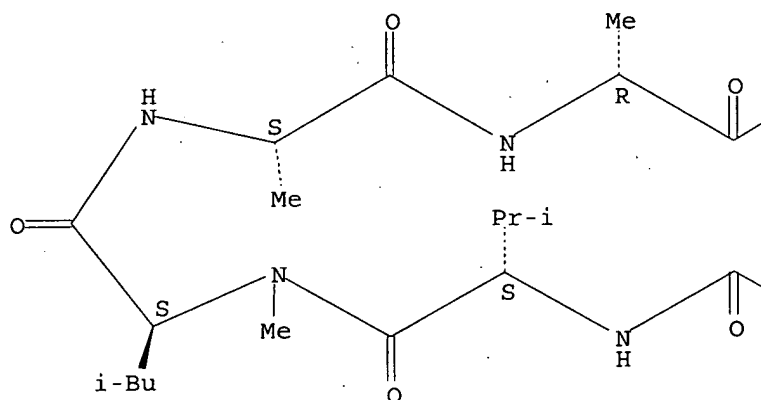
(preparation of **cyclosporin** analogs for treatment of lung diseases)

RN 59865-13-3 HCAPLUS

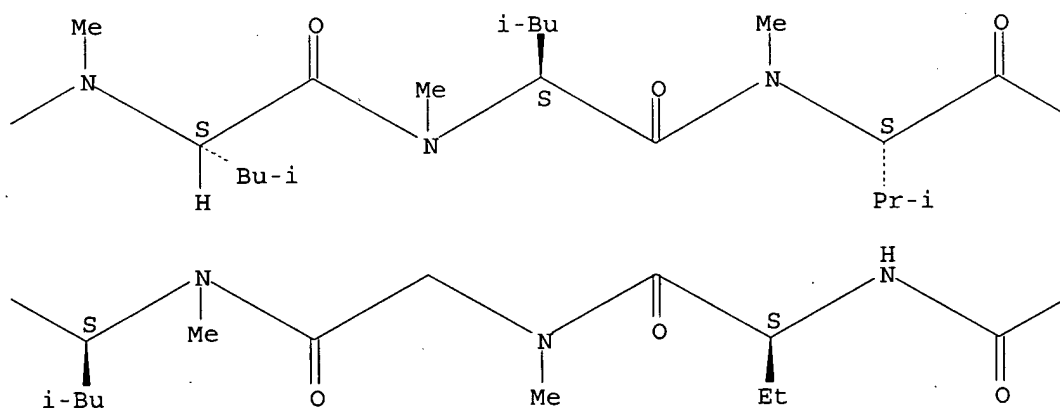
CN Cyclosporin A (9CI) (CA INDEX NAME)

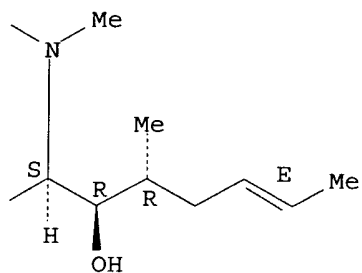
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

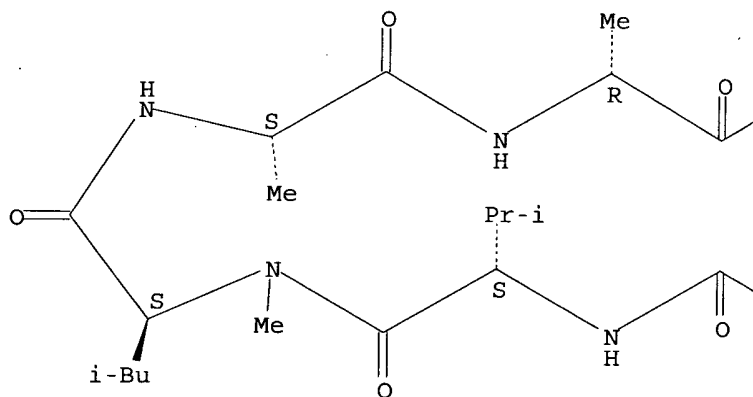




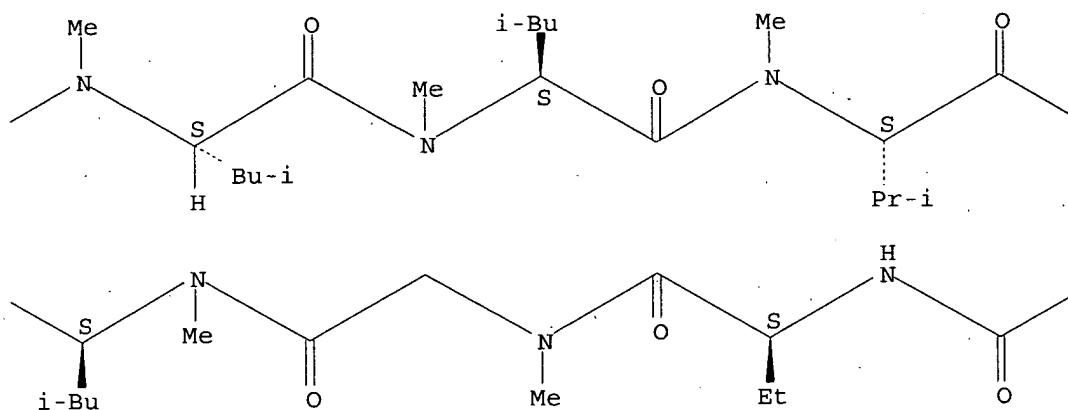
RN 502998-21-2 HCAPLUS

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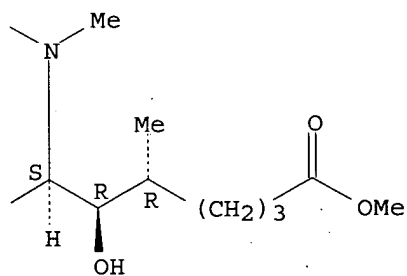
Absolute stereochemistry.



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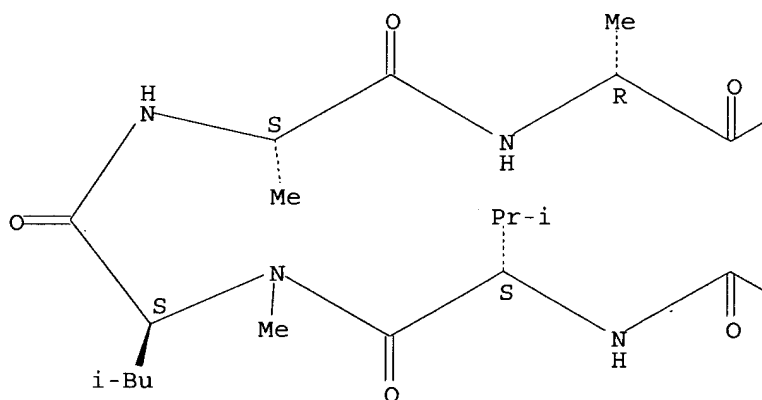
PAGE 1-C



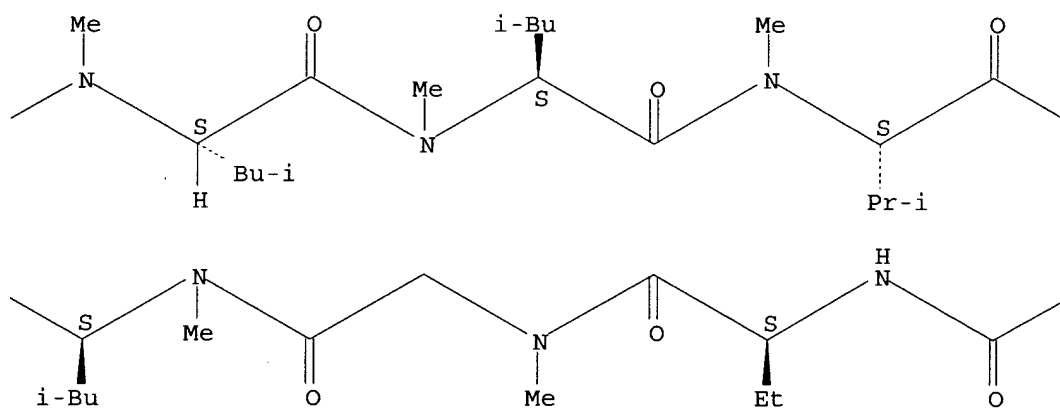
RN 502998-23-4 HCAPLUS

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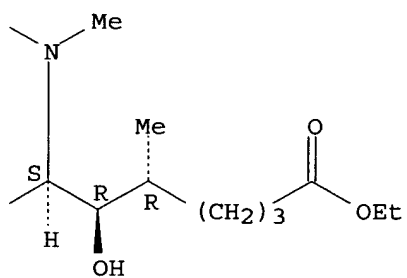
Absolute stereochemistry.



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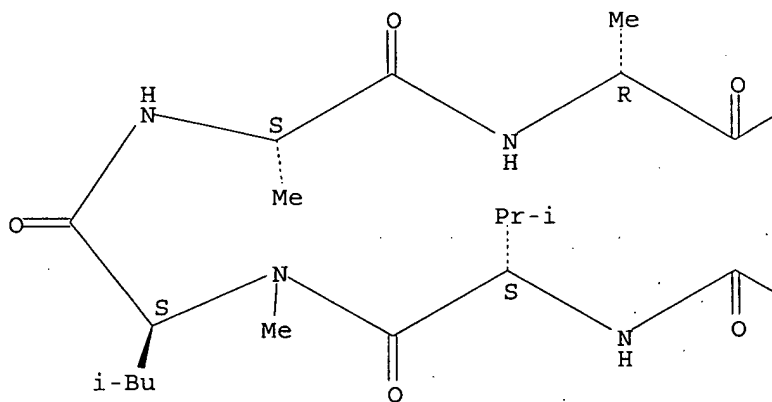
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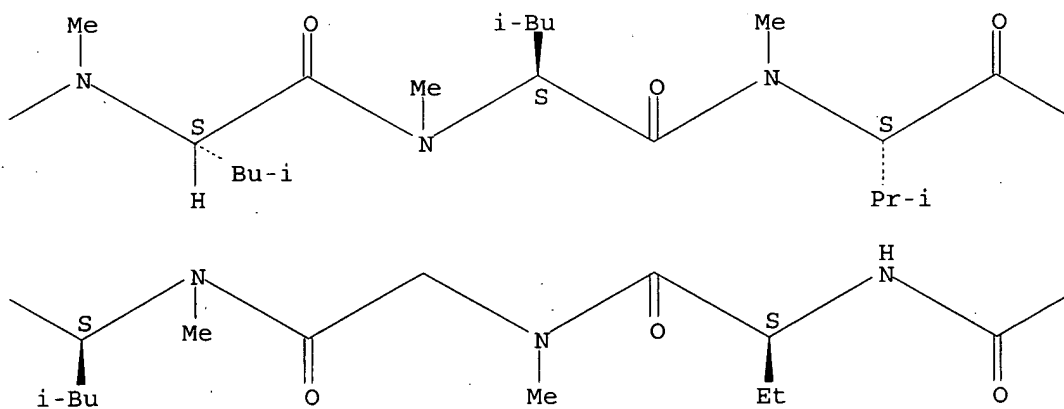
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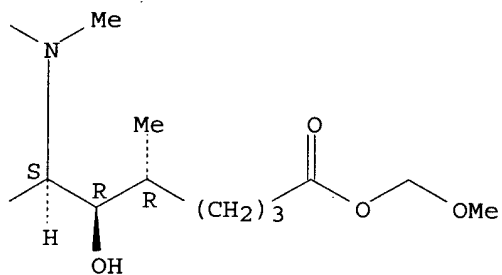
Absolute stereochemistry.

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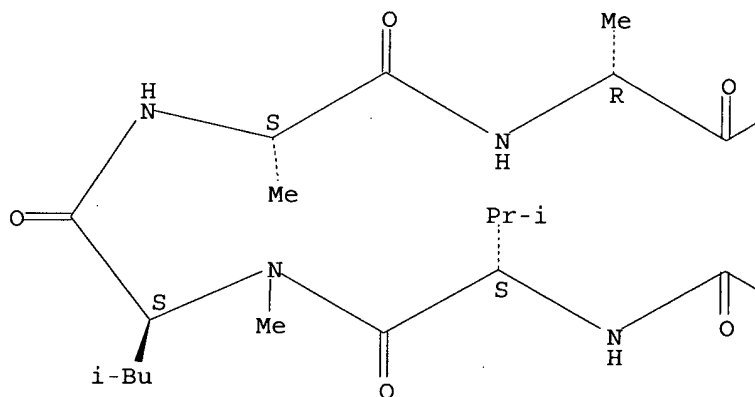




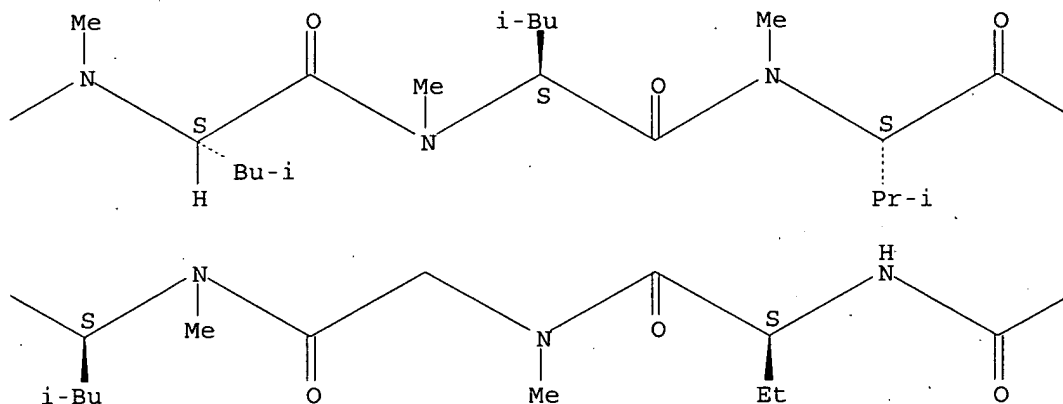
RN 502998-26-7 HCAPLUS

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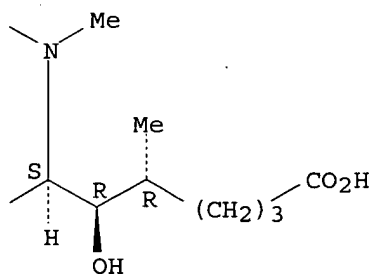
Absolute stereochemistry.



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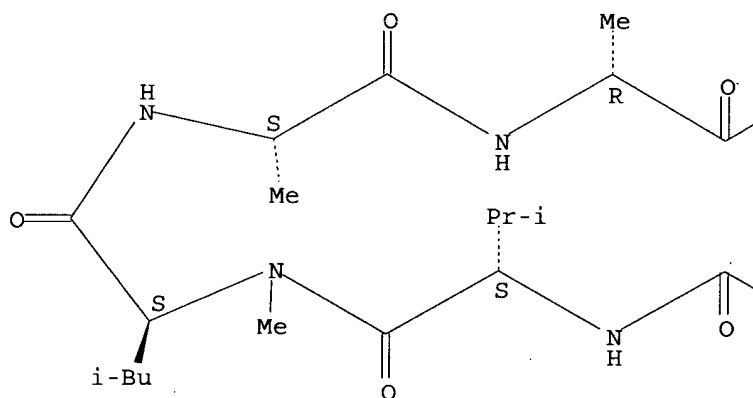


RN 510741-22-7 HCAPLUS

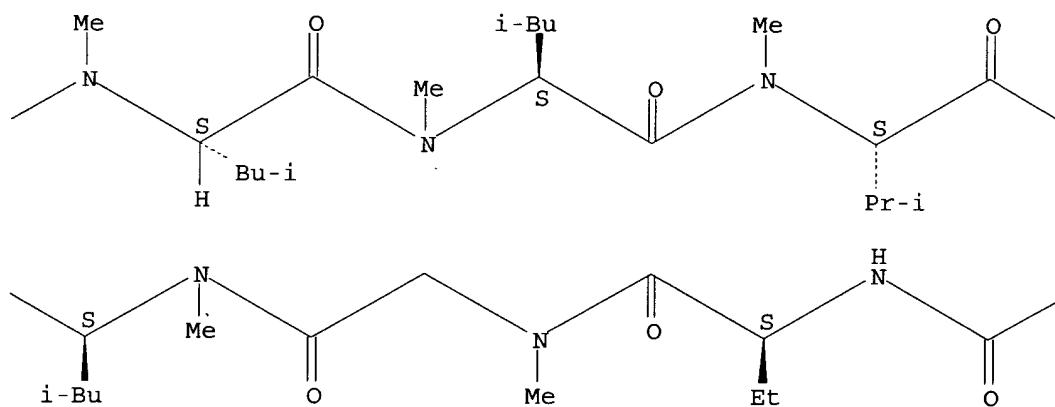
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

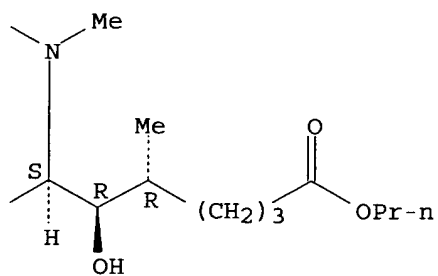
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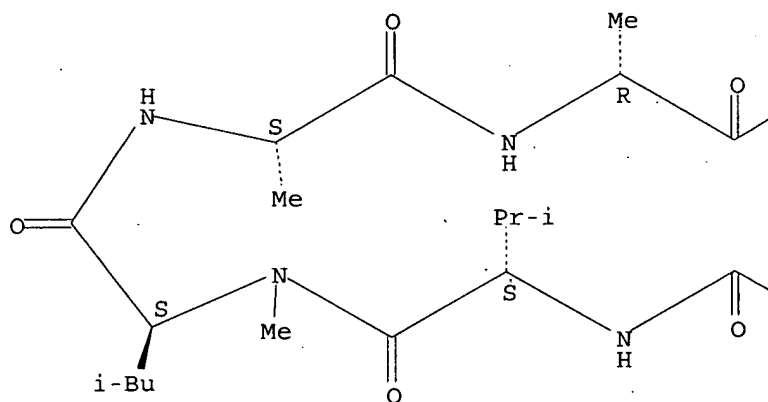


RN 510741-23-8 HCAPLUS

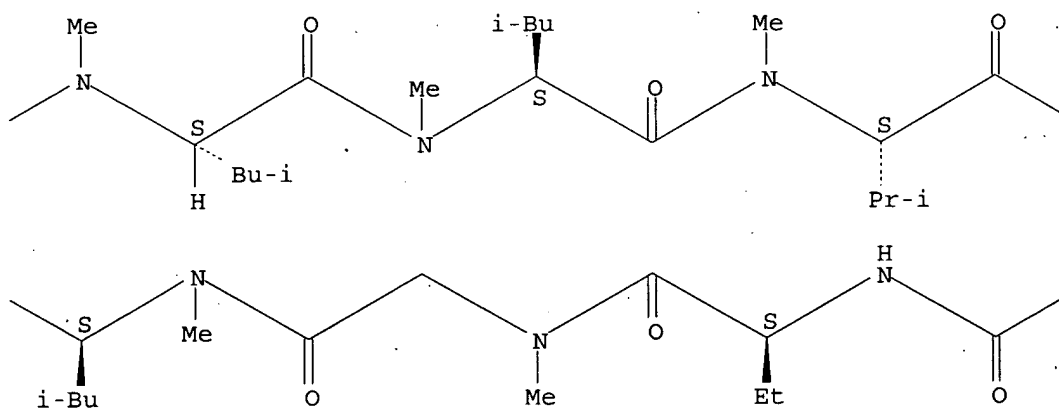
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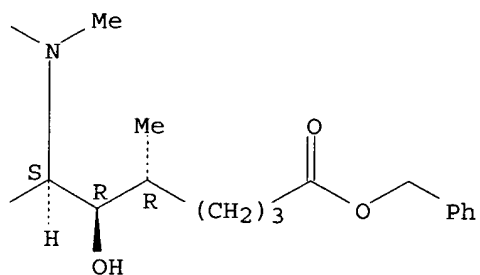
Absolute stereochemistry.

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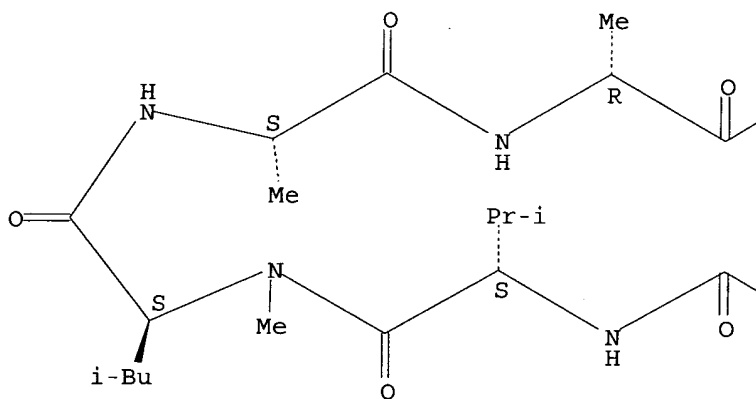


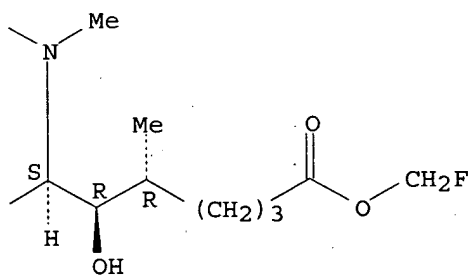
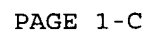


RN 510741-25-0 HCAPLUS

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Absolute stereochemistry.

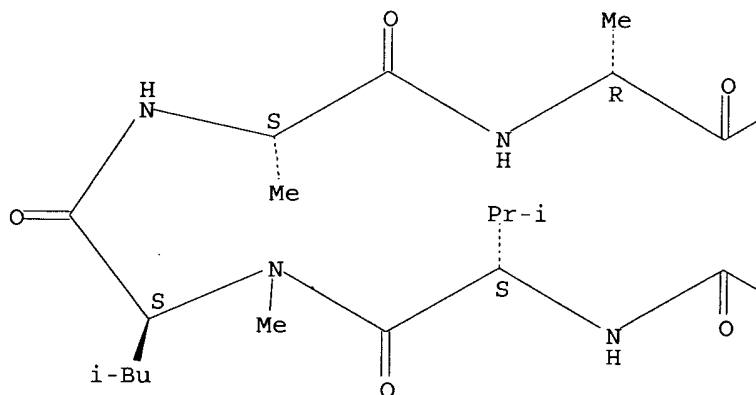




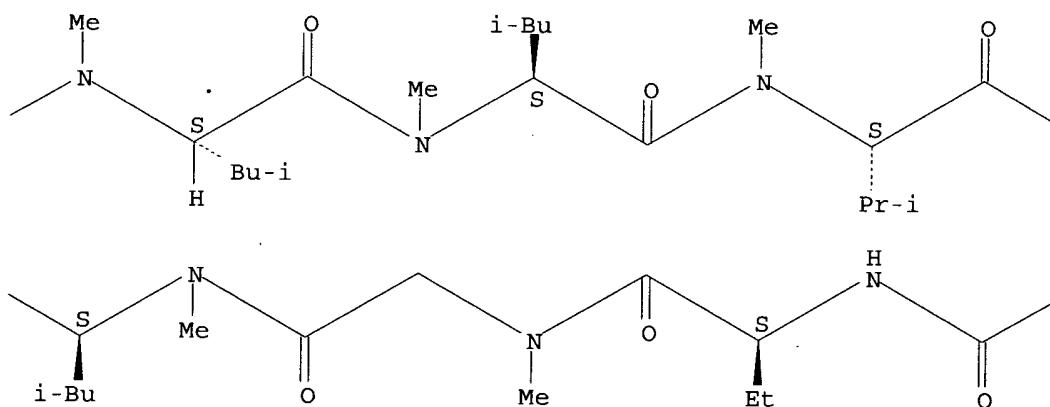
RN	510741-27-2	HCAPLUS
CN	Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, difluoromethyl ester (9CI) (CA INDEX NAME)	

Absolute stereochemistry.

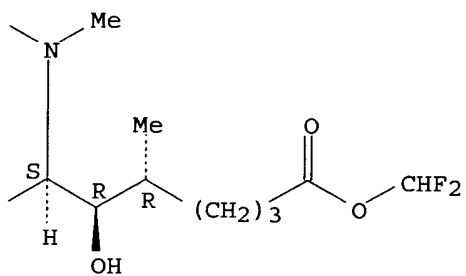
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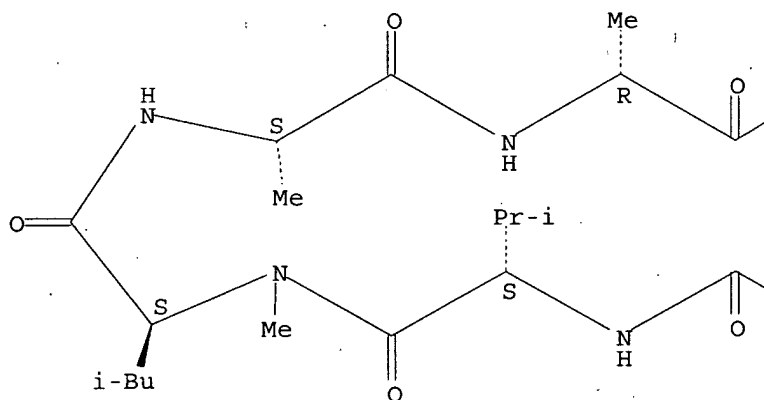


RN 510741-28-3 HCAPLUS

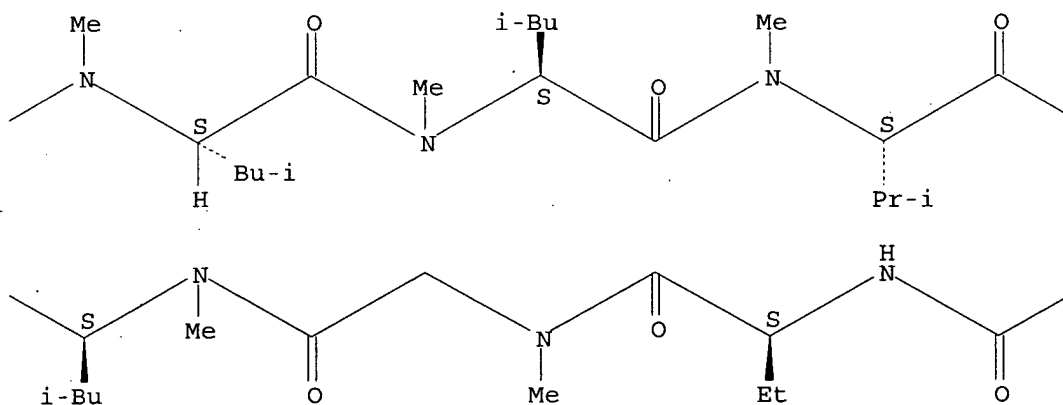
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, trifluoromethyl ester (9CI) (CA INDEX NAME)

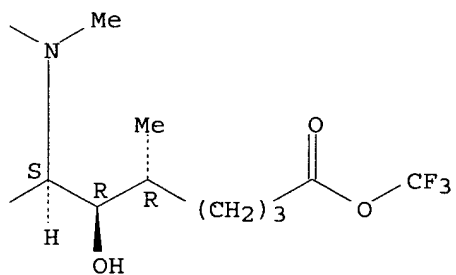
Absolute stereochemistry.

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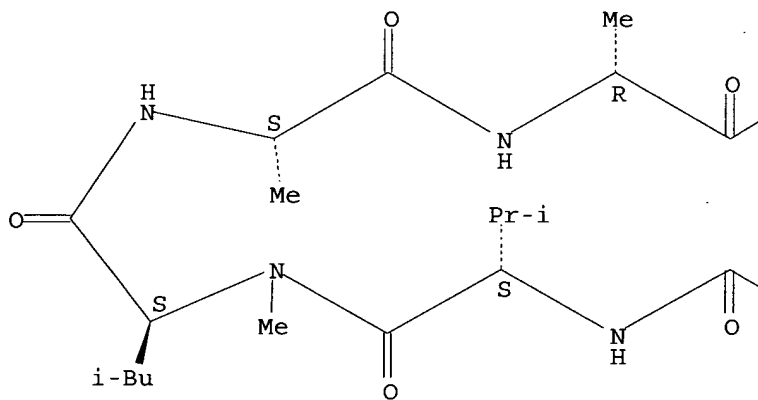




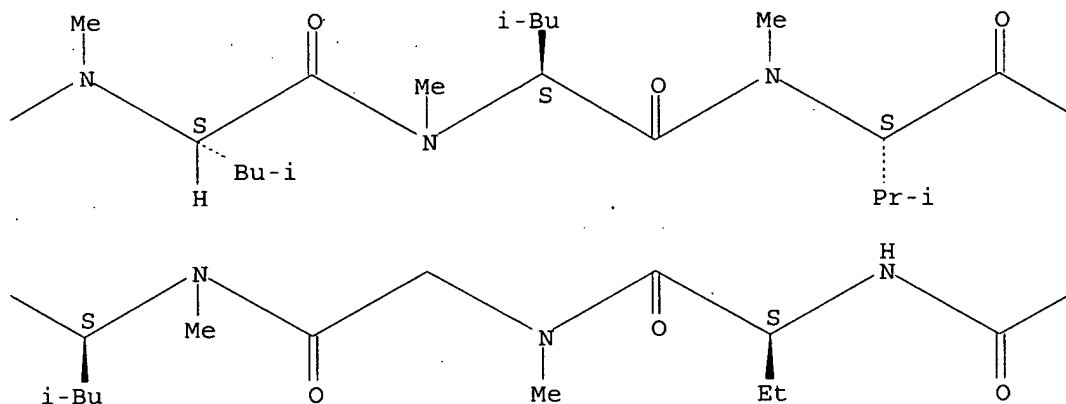
RN 510741-30-7 HCAPLUS

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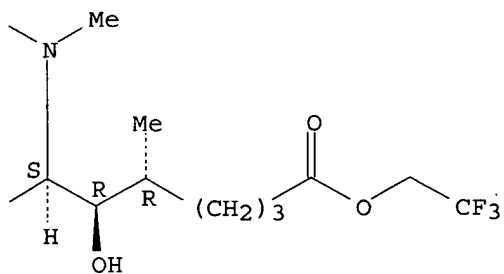
Absolute stereochemistry.



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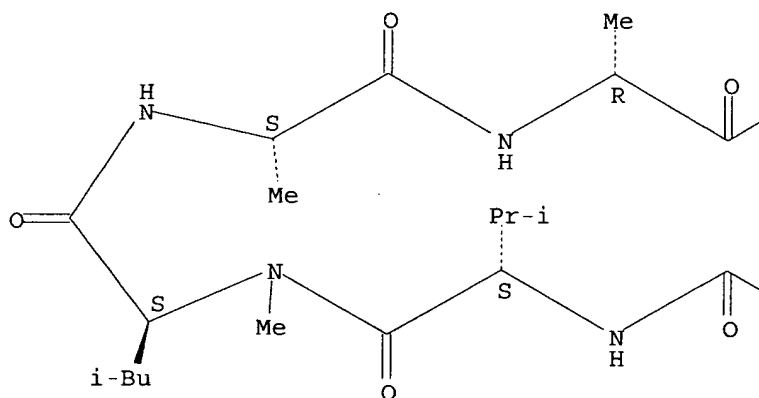


RN 510741-32-9 HCAPLUS

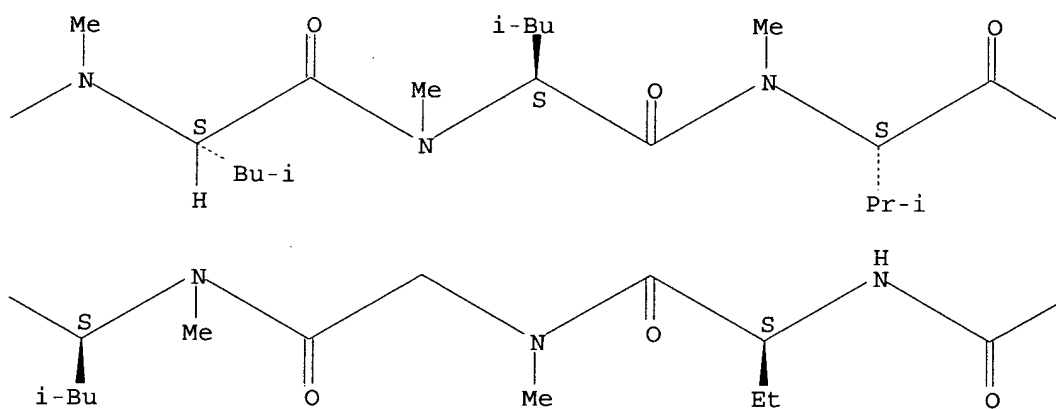
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, chloromethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

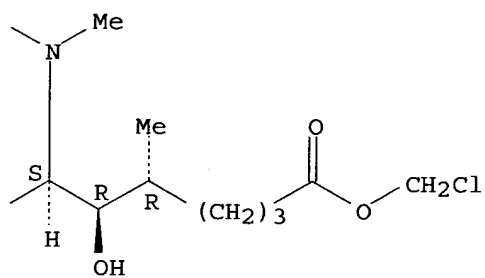
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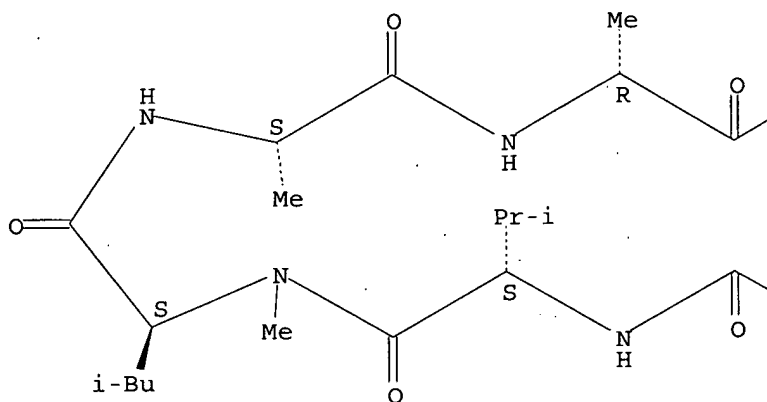


RN 510741-34-1 HCAPLUS

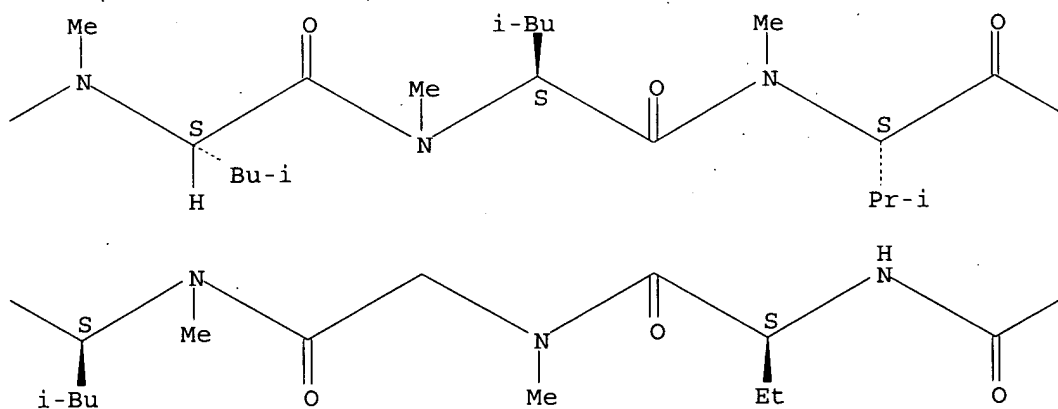
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, (2-methoxyethoxy)methyl ester (9CI) (CA INDEX NAME)

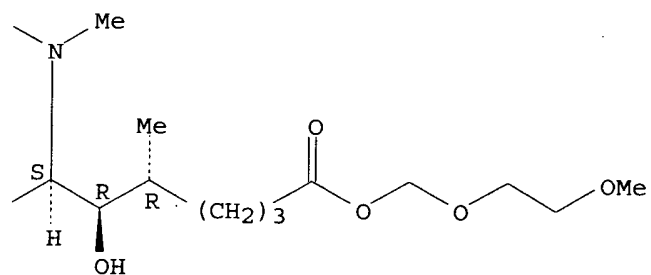
Absolute stereochemistry.

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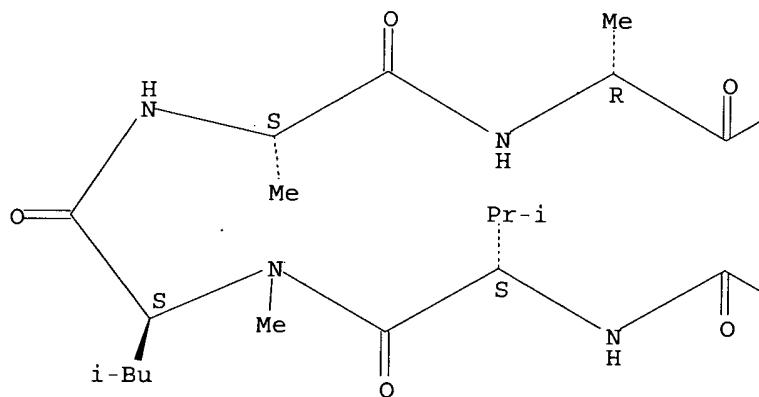




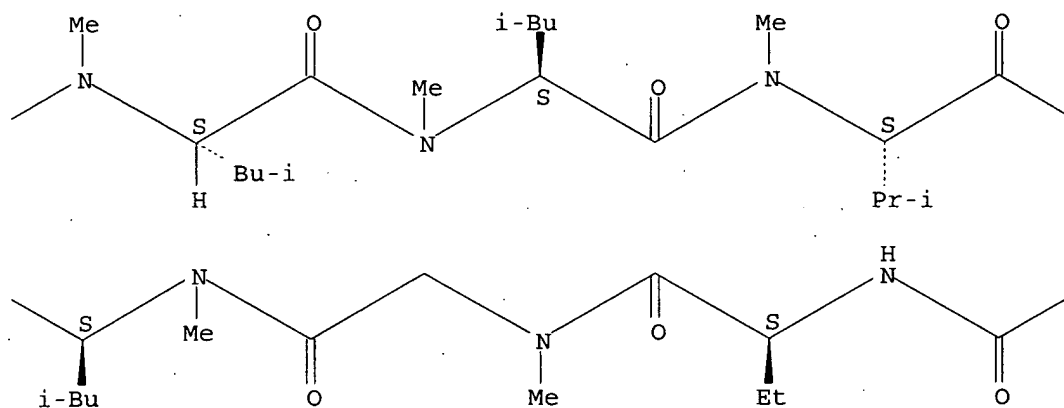
RN 510741-35-2 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-8-oxo-8-
[(phenylmethyl)thio]octanoic acid]- (9CI) (CA INDEX NAME)

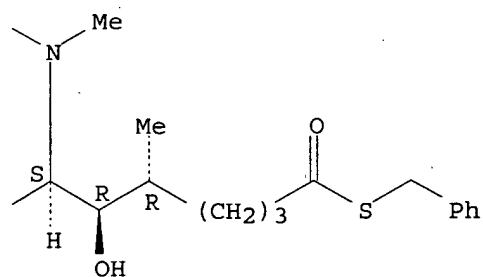
Absolute stereochemistry.



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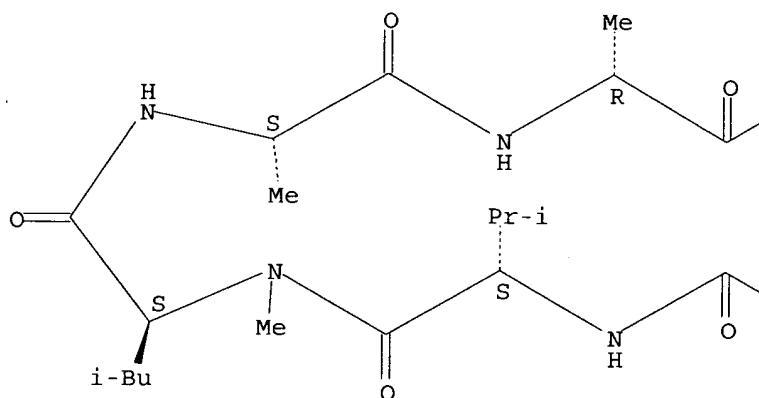


RN 510741-36-3 HCAPLUS

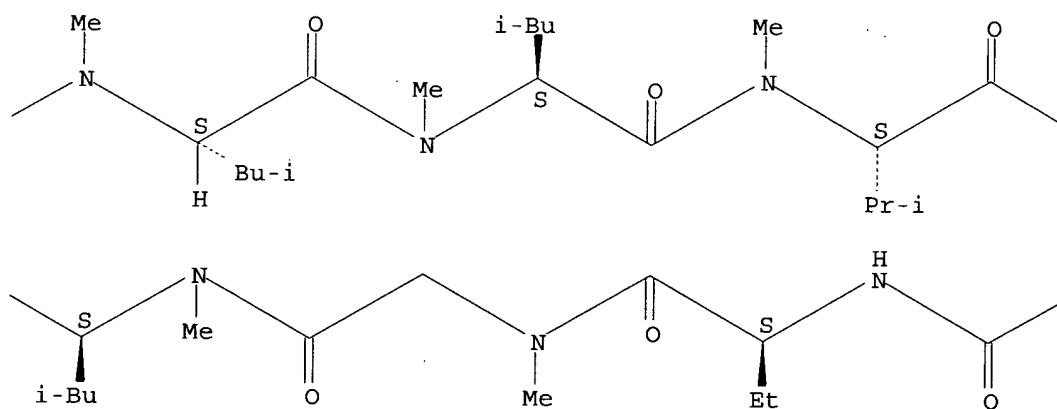
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)undecanedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

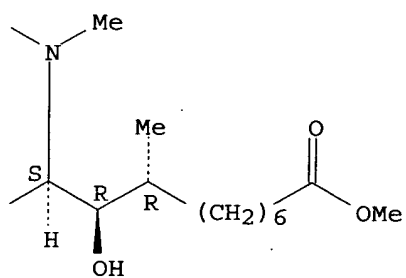
PAGE 1-A



PAGE 1-B



PAGE 1-C

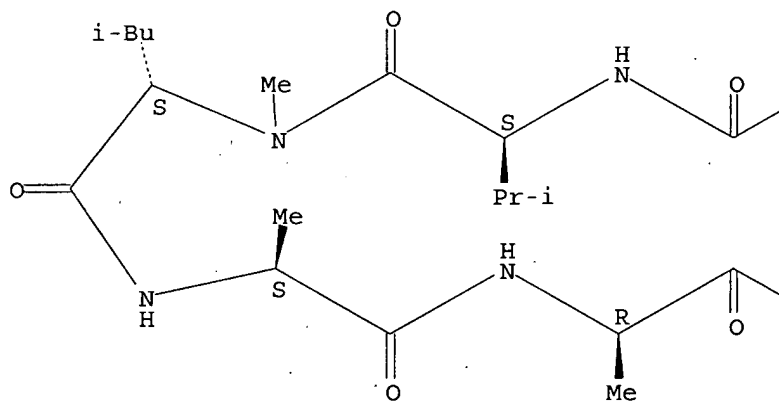


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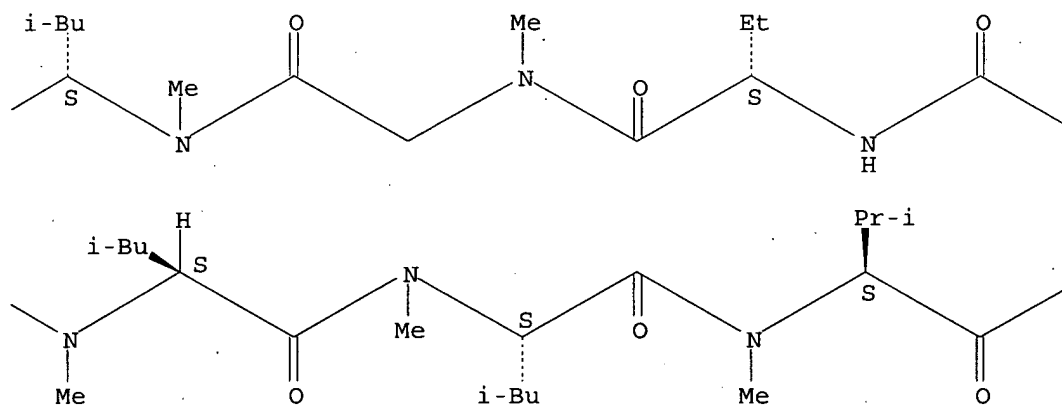
CN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanedioic acid]-, anhydride with 9H-fluoren-9-ylmethyl hydrogen carbonate (9CI) (CA INDEX NAME)

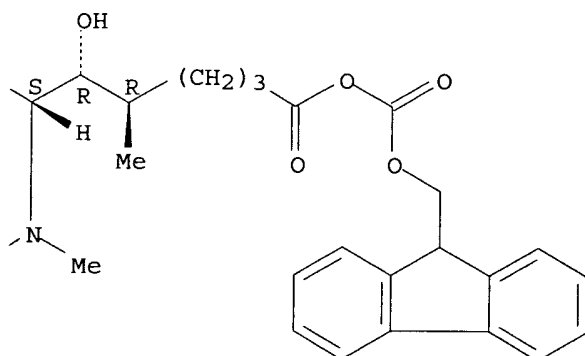
Absolute stereochemistry.

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IT 122547-85-7 457612-98-5

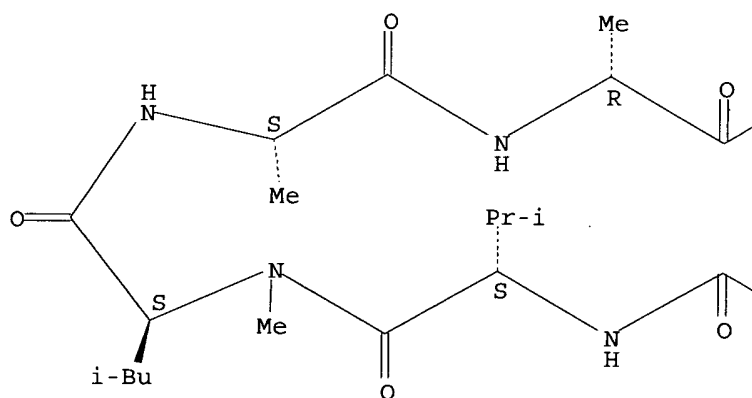
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of **cyclosporin** analogs for treatment of lung diseases)

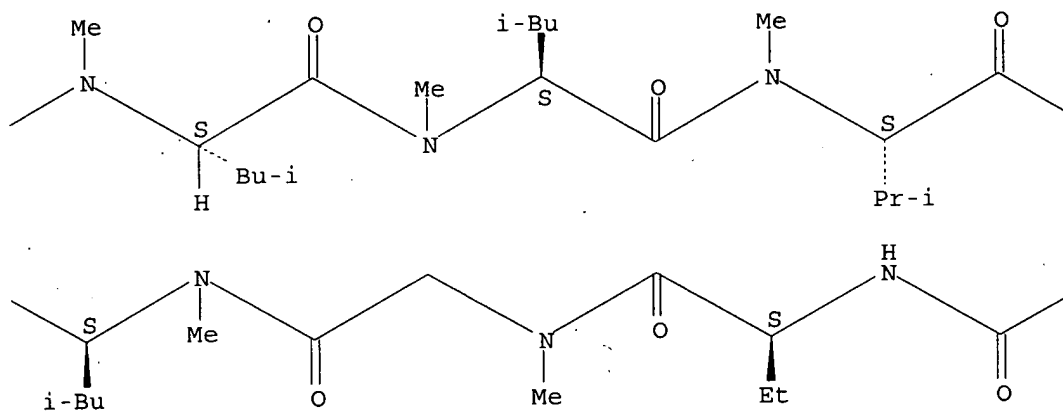
RN 122547-85-7 HCAPLUS

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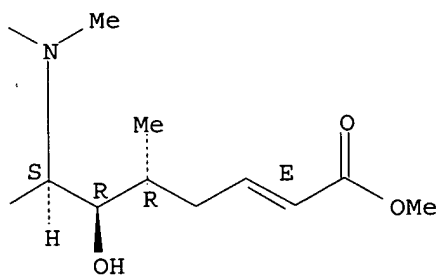
Absolute stereochemistry.
Double bond geometry as shown.



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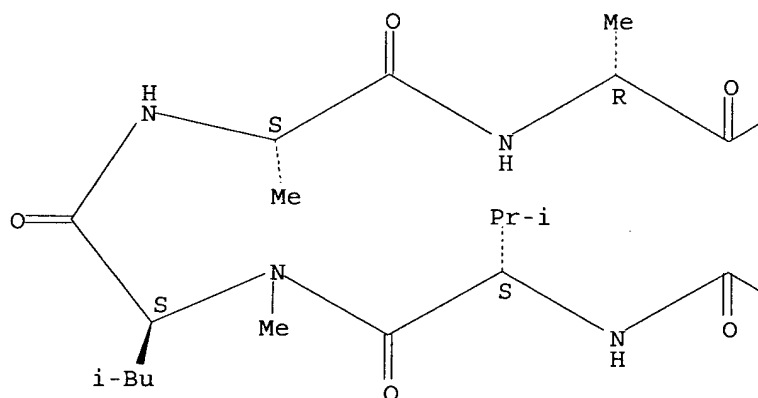


RN 457612-98-5 HCAPLUS

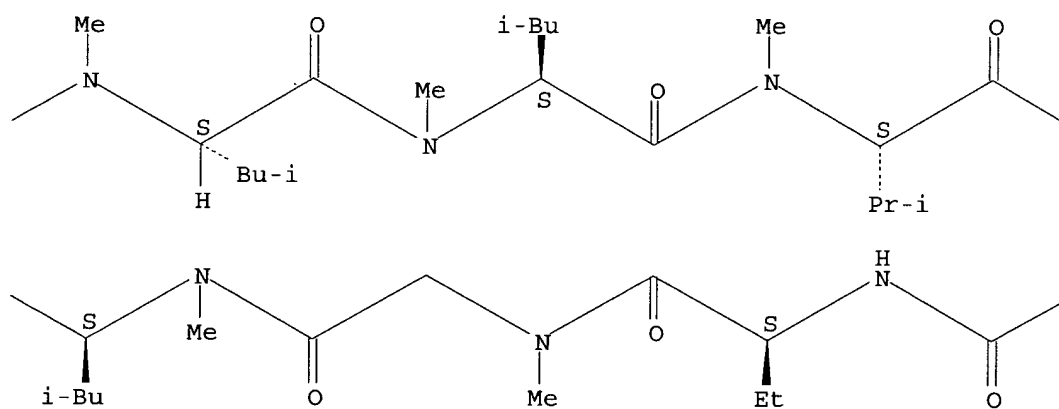
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

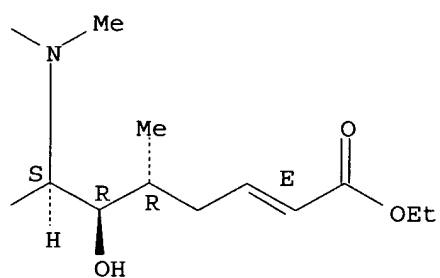
PAGE 1-A



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L17 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:184221 HCAPLUS

TITLE: Synthesis and biological evaluation of novel
cyclosporin A derivatives with potentially
improved therapeutic indexAUTHOR(S): Chen, Jason S.; Lazarova, Tsvetelina I.; Hamann,
Blake; Kang, Jane M.; Homuth-Trombino, Daniela;
Hoffmann, Ethan; McClure, Chris; Eckstein, Jens;
Or, Yat SunCORPORATE SOURCE: Department of Chemistry, Enanta Pharmaceuticals, Inc.,
Watertown, MA, 02472, USASOURCE: Abstracts of Papers, 225th ACS National Meeting, New
Orleans, LA, United States, March 23-27, 2003 (2003),
MEDI-255. American Chemical Society: Washington, D.
C.

CODEN: 69DSA4

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Short-term **Cyclosporin A** (CsA) use is well tolerated by humans,
but its chronic use is limited due to its toxicity profile. Both CsA and
its metabolites are thought to contribute to the toxicity. We have
synthesized a series of novel CsA derivs. by using an olefin cross
metathesis reaction of CsA with styrenes and heteroarom. styrene analogs.
The CsA derivs. show activity in a calcineurin inhibition assay with IC50s
noticeably better than that of the parent compound. Furthermore, since the
primary metabolism site of **Cyclosporin A** has been blocked in the new
CsA derivs., these derivs. will be metabolized differently and therefore
have a different, potentially improved toxicity profile. The synthesis,
characterization, and biol. evaluation of the CsA derivs. will be
presented.

L17 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:72696 HCAPLUS

DOCUMENT NUMBER: 138:248196

TITLE: Synthesis and Biological Evaluation of Novel
Cyclosporin A Analogues: Potential Soft Drugs
for the Treatment of Autoimmune DiseasesAUTHOR(S): Lazarova, Tsvetelina; Chen, Jason S.; Hamann, Blake;
Kang, Jane M.; Homuth-Trombino, Daniela; Han, Feng;
Hoffmann, Ethan; McClure, Christopher; Eckstein, Jens;
Or, Yat Sun

CORPORATE SOURCE: Enanta Pharmaceuticals, Watertown, MA, 02472, USA

SOURCE: Journal of Medicinal Chemistry (2003), 46(5), 674-676

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Cyclosporin A** is effective in the treatment of asthma patients,
but its chronic use is limited by toxicity. Novel **cyclosporin A**
analogues were synthesized utilizing the olefin metathesis reaction and
evaluated in a calcineurin A inhibition assay. The novel analogs
demonstrated activity comparable to activity of the parent mol. and are
potential soft drugs.

IT 59865-13-3, **Cyclosporin A**RL: ADV (Adverse effect, including toxicity); RCT (Reactant); THU
(Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent);
USES (Uses)(synthesis and biol. evaluation of novel **cyclosporin A**

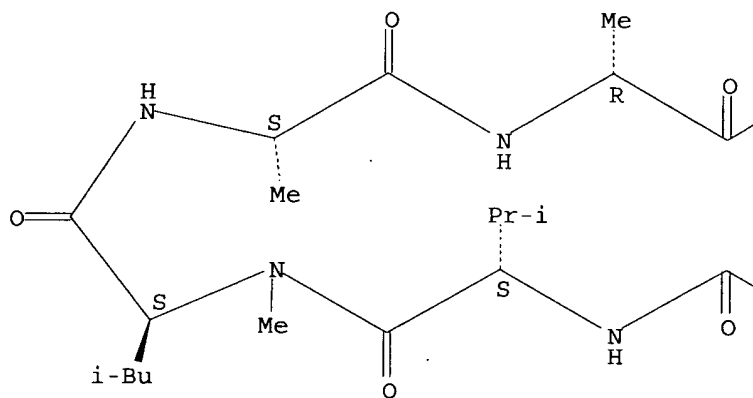
analogues as potential soft drugs for treatment of autoimmune diseases)

RN 59865-13-3 HCAPLUS

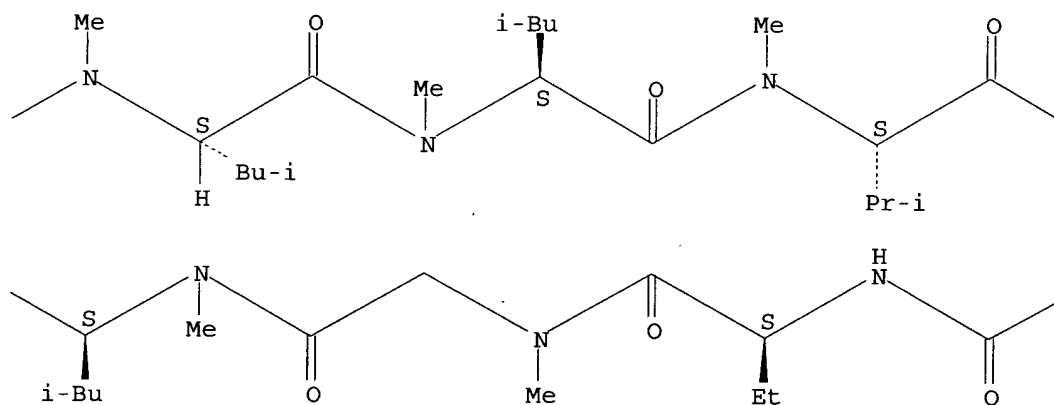
CN Cyclosporin A (9CI) (CA INDEX NAME)

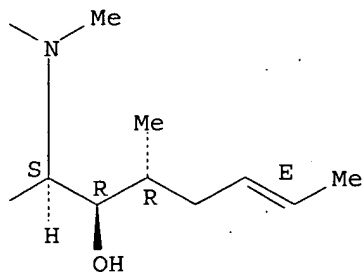
Absolute stereochemistry.
Double bond geometry as shown.

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IT 100364-58-7P 122547-85-7P 457612-98-5P

457613-07-9P 502998-17-6P 502998-19-8P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(synthesis and biol. evaluation of novel **cyclosporin A**

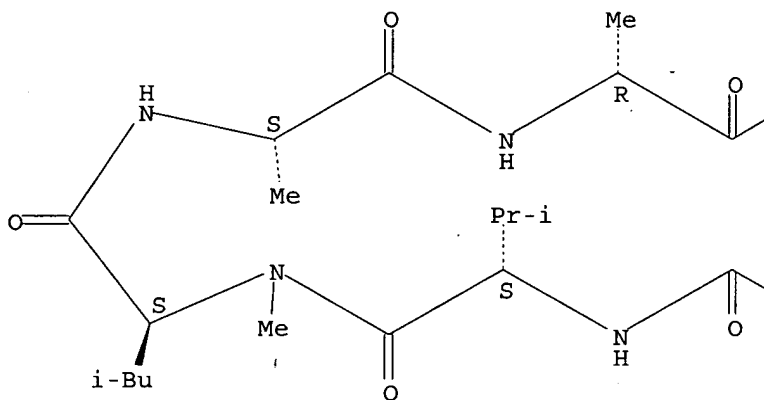
analogs as potential soft drugs for treatment of autoimmune diseases)

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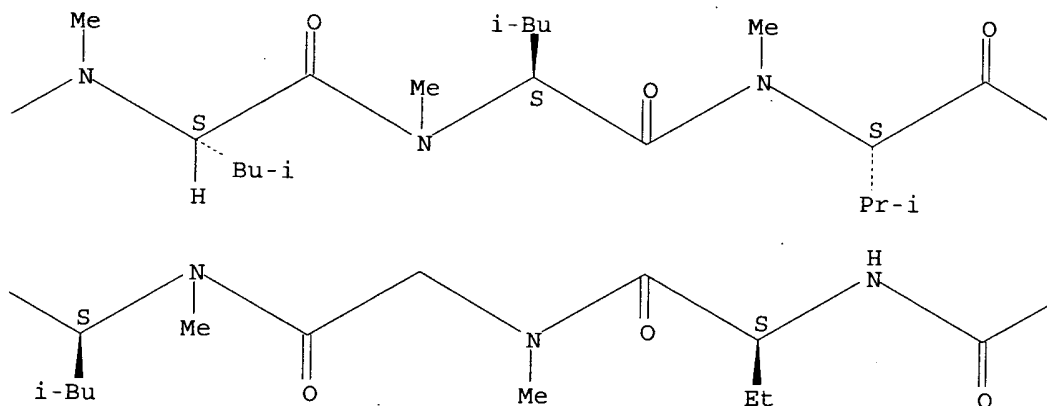
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

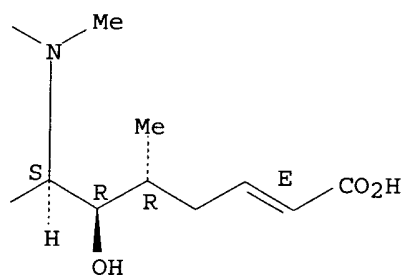
Double bond geometry as shown.



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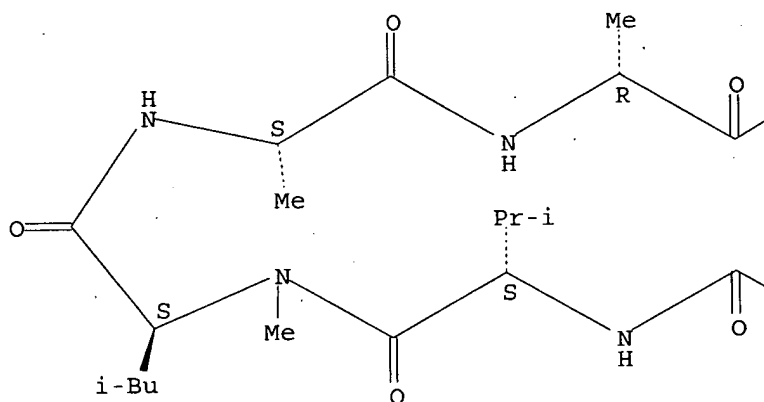


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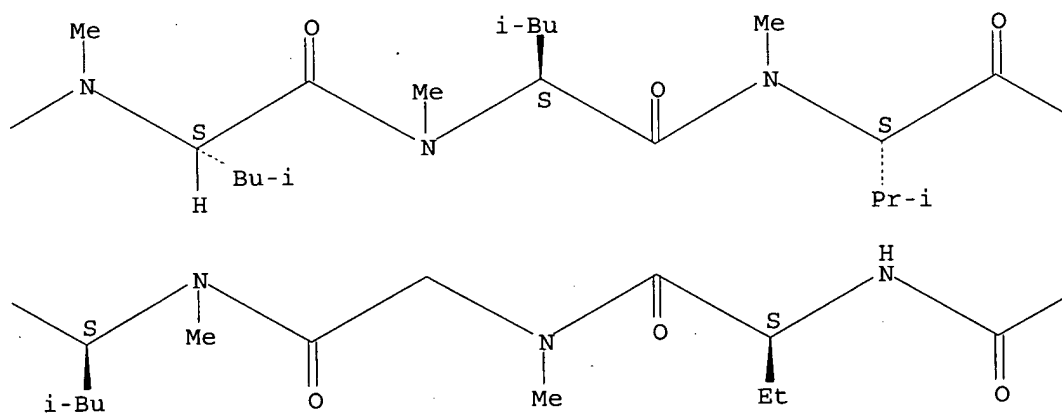
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Double bond geometry as shown.

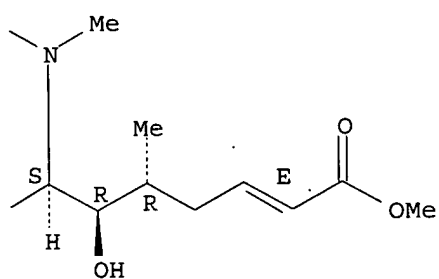
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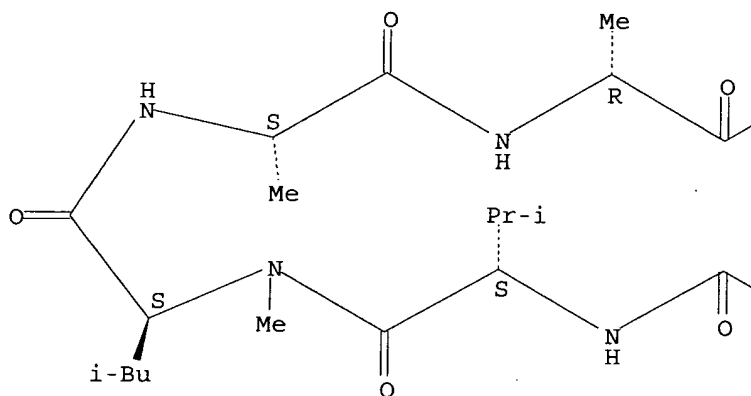


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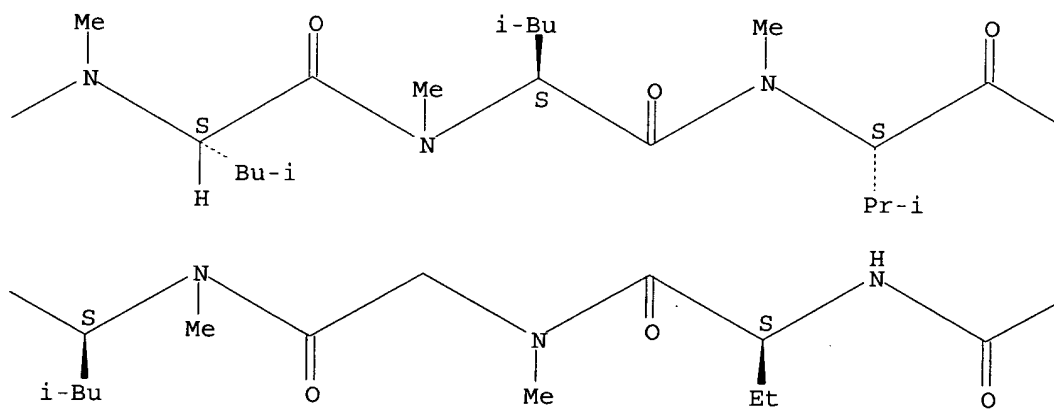
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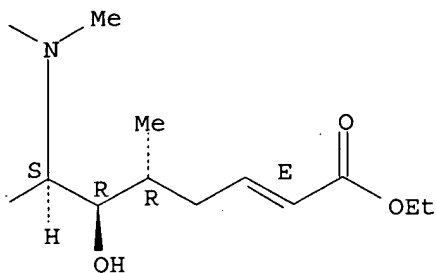
Absolute stereochemistry.
Double bond geometry as shown.

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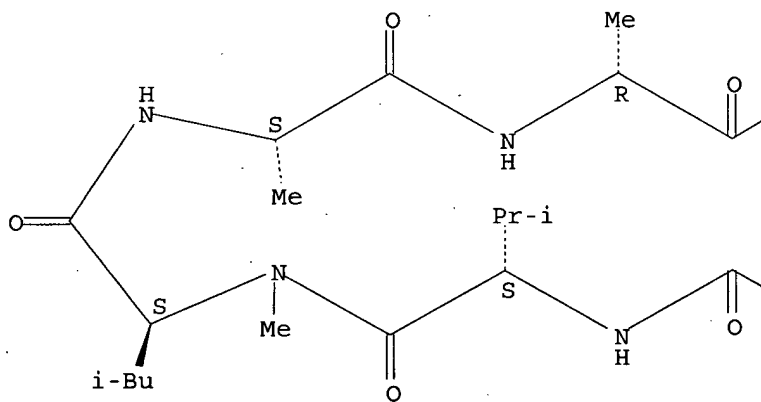




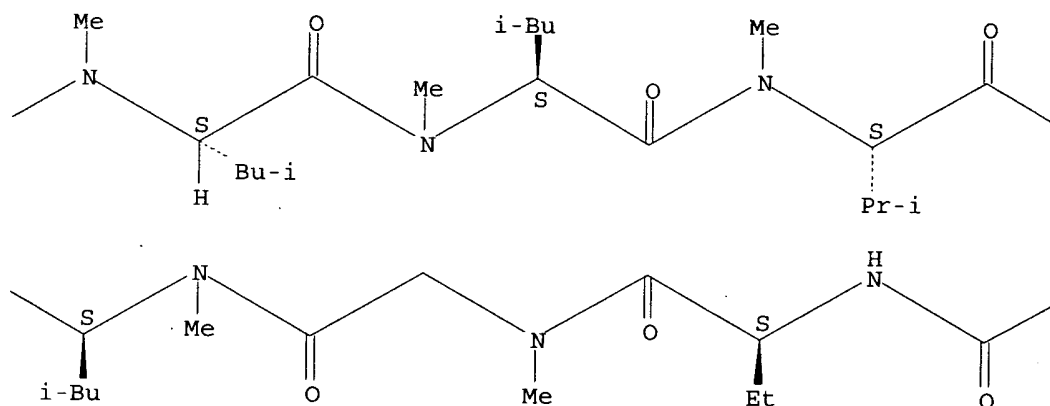
RN 457613-07-9 HCAPLUS

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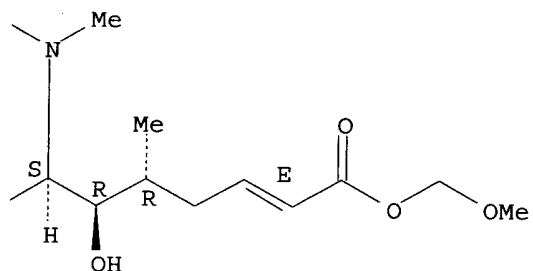
Absolute stereochemistry.
Double bond geometry as shown.



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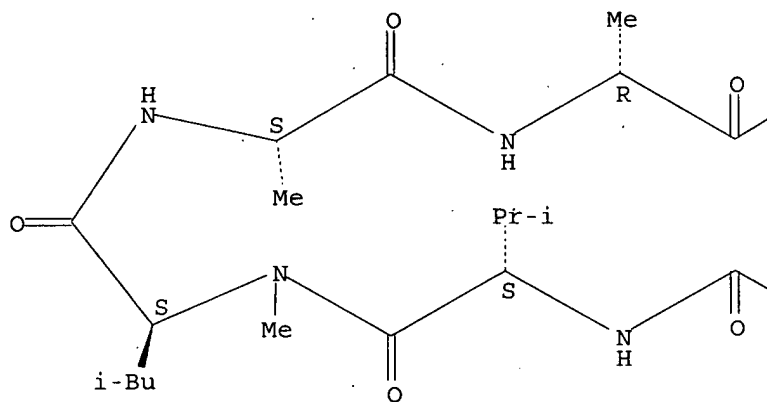


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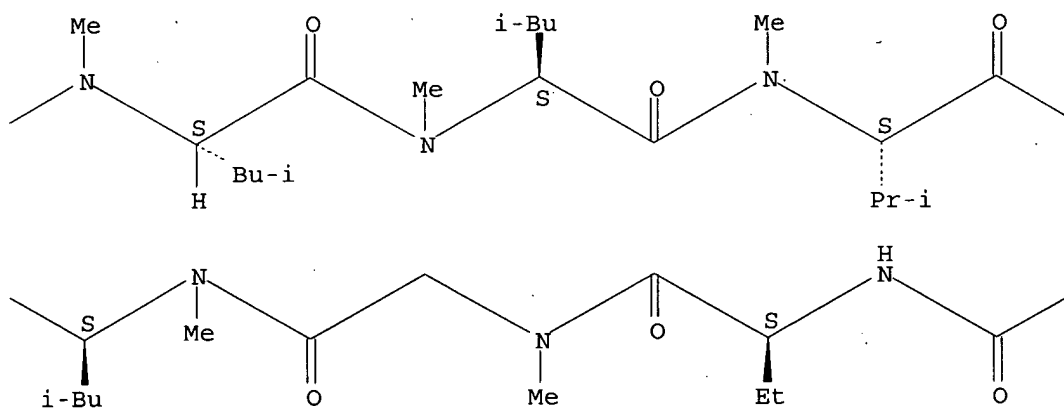
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-8-(2-fluoroethoxy)-3-hydroxy-4-methyl-2-(methylamino)-8-oxo-6-octenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

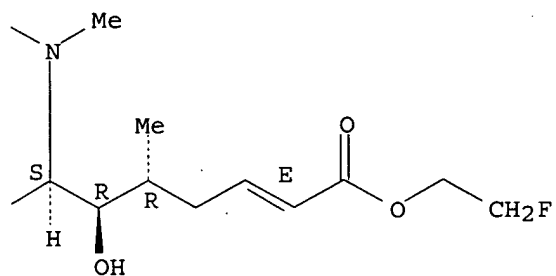
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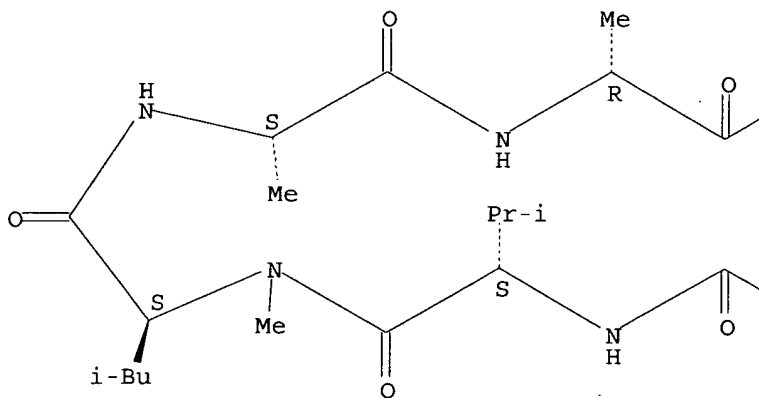


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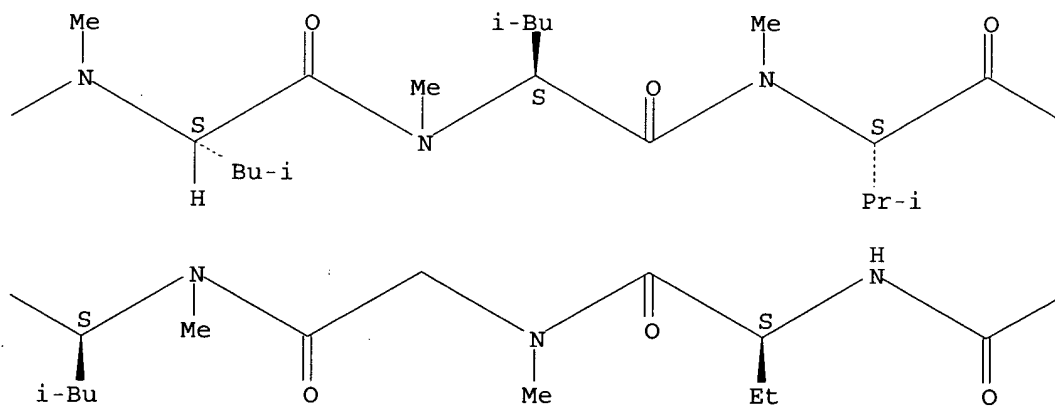
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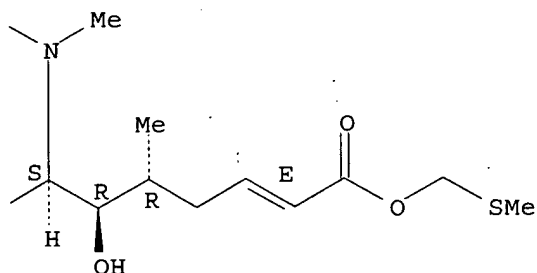
Absolute stereochemistry.
Double bond geometry as shown.

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IT 502998-21-2P 502998-23-4P 502998-24-5P

502998-26-7P 502998-28-9P 502998-30-3P

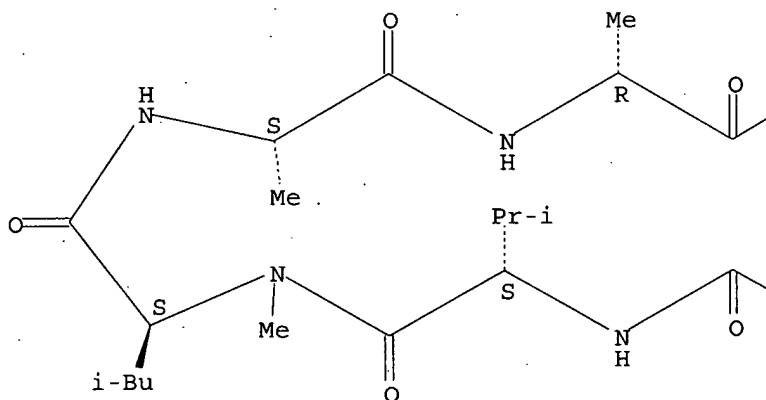
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
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(synthesis and biol. evaluation of novel **cyclosporin A**
analogs as potential soft drugs for treatment of autoimmune diseases)

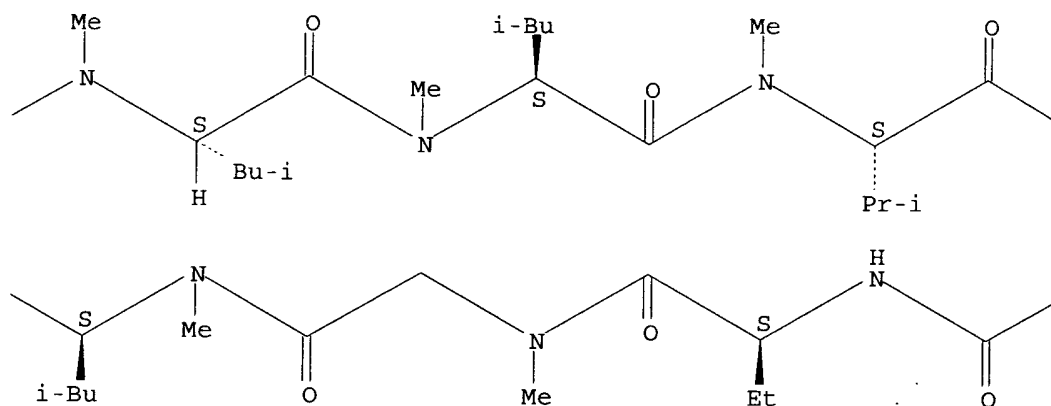
RN 502998-21-2 HCAPLUS

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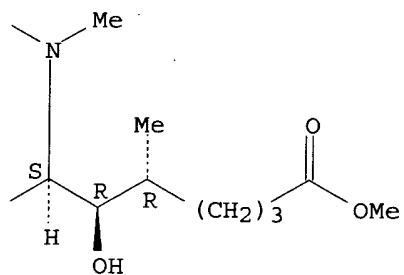
Absolute stereochemistry.



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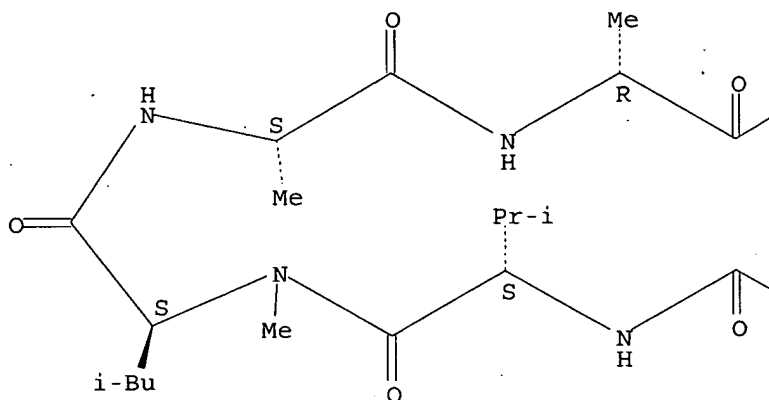


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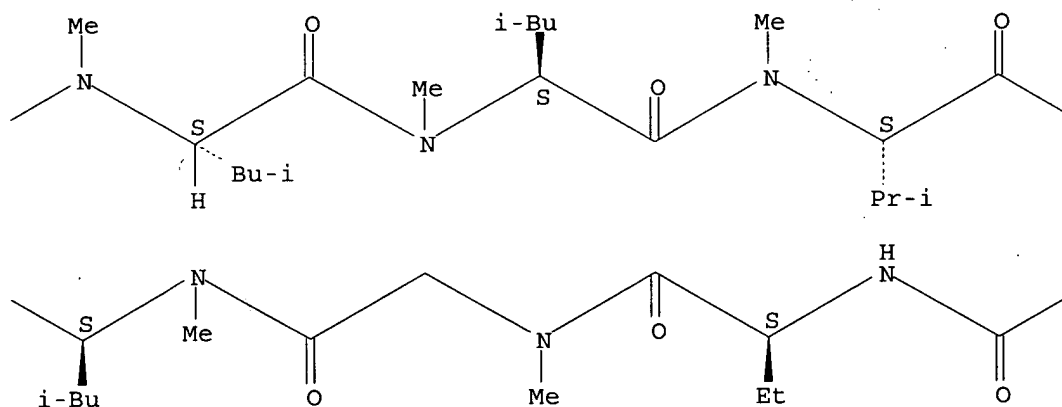
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Absolute stereochemistry.

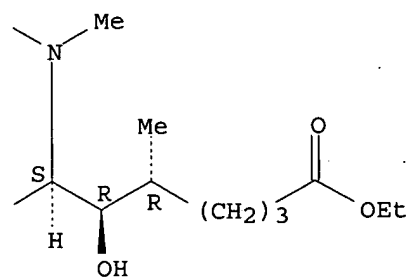
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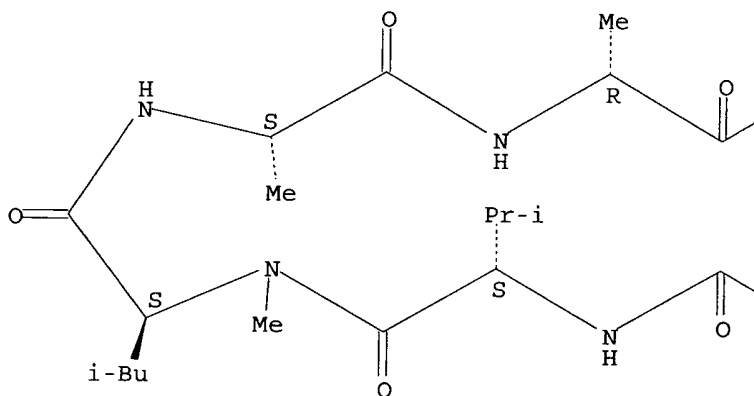


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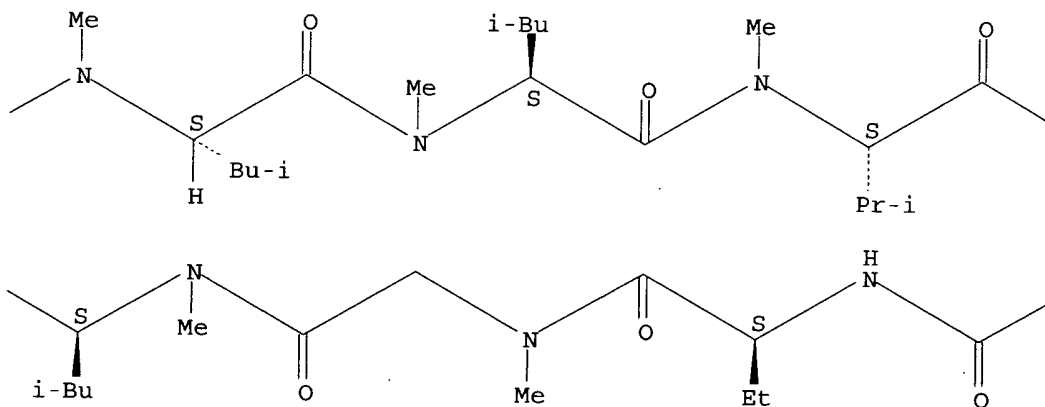
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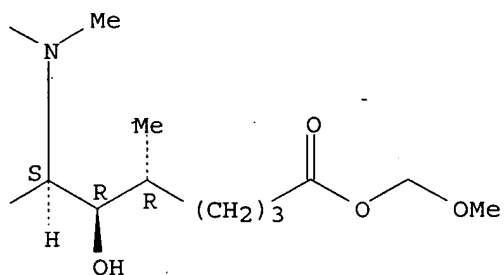
Absolute stereochemistry.

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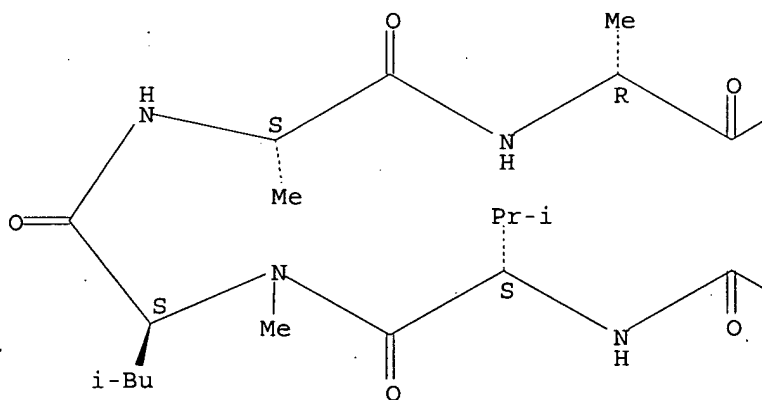




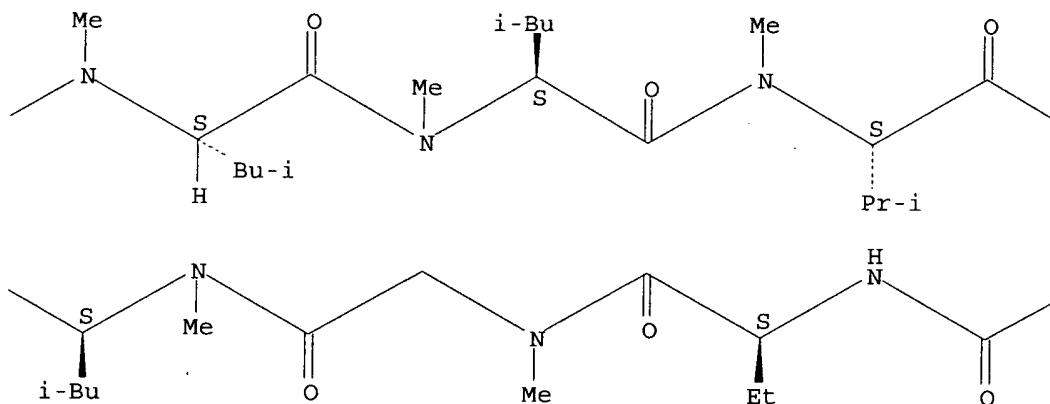
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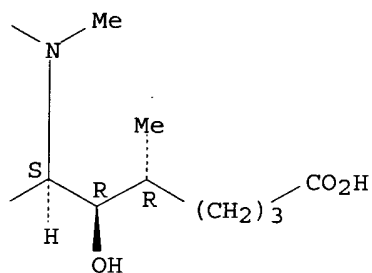
Absolute stereochemistry.



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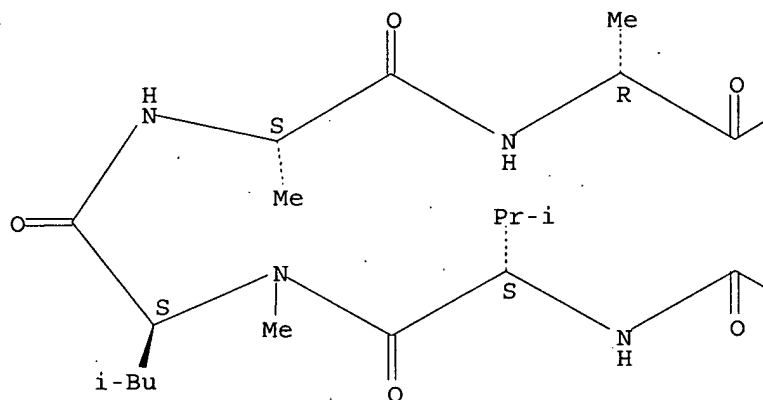


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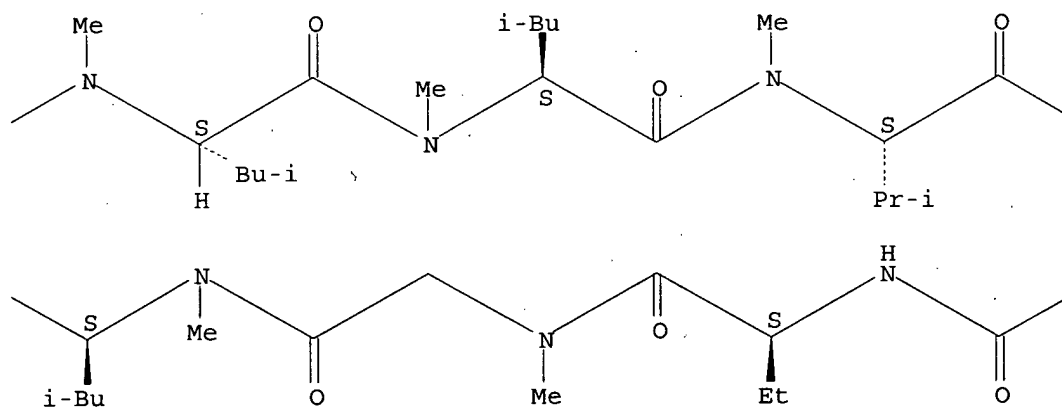
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Absolute stereochemistry.

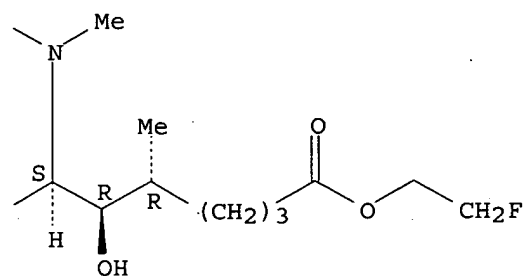
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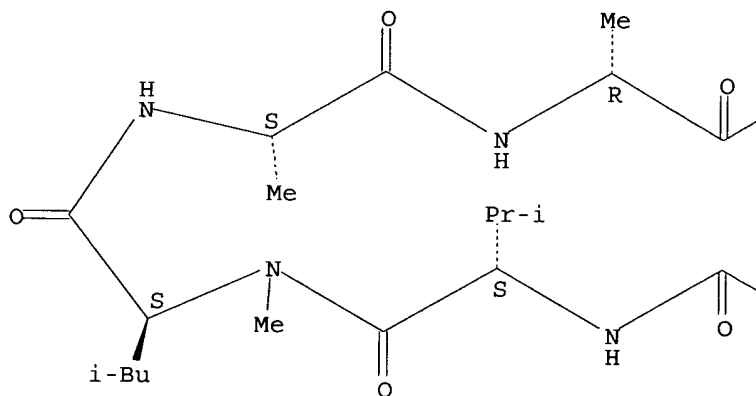


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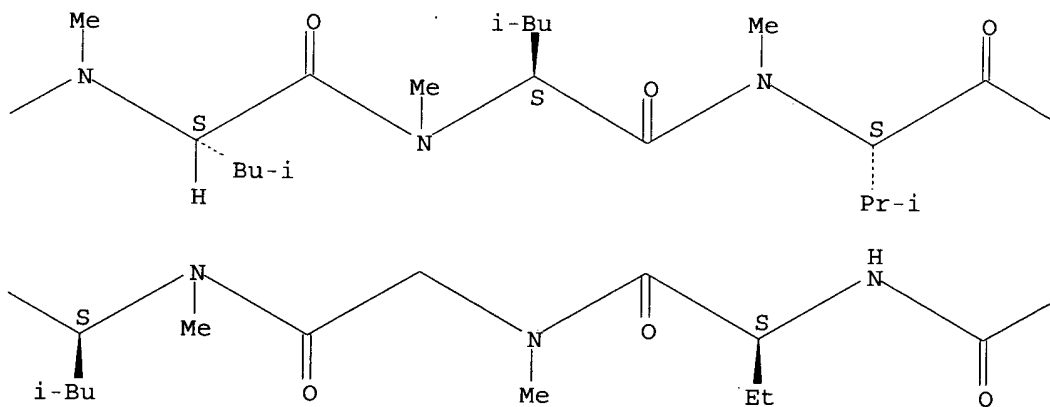
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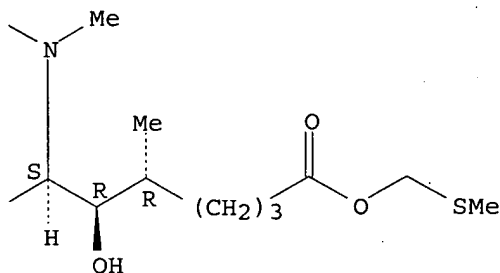
Absolute stereochemistry.

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REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:695724 HCAPLUS

DOCUMENT NUMBER: 137:226601

TITLE: Cyclosporins for the treatment of respiratory diseases

INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Hamann, Blake Christopher

PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069902	A2	20020912	WO 2002-US6541	20020305
WO 2002069902	A3	20030417		
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RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
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PRIORITY APPLN. INFO.:			US 2001-800856	A 20010305
			WO 2002-US6541	W 20020305

OTHER SOURCE(S): MARPAT 137:226601

AB Novel semisynthetic **cyclosporin** analogs containing different amino acids are synthesized for use as pharmaceuticals. The compds. can be used for the treatment of asthma, allergic rhinitis, bronchitis, etc. Thus, **cyclosporin** analogs were prepared and their immunosuppressant activity was determined by using the inhibition of the phosphate activity as the parameter.

IT 100364-58-7P 457612-98-5P 457612-99-6P
 457613-00-2P 457613-01-3P 457613-02-4P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

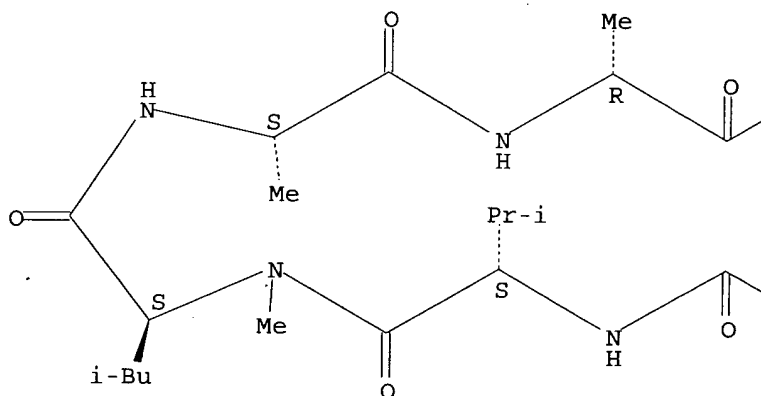
(**cyclosporins** for the treatment of respiratory diseases)

RN 100364-58-7 HCAPLUS

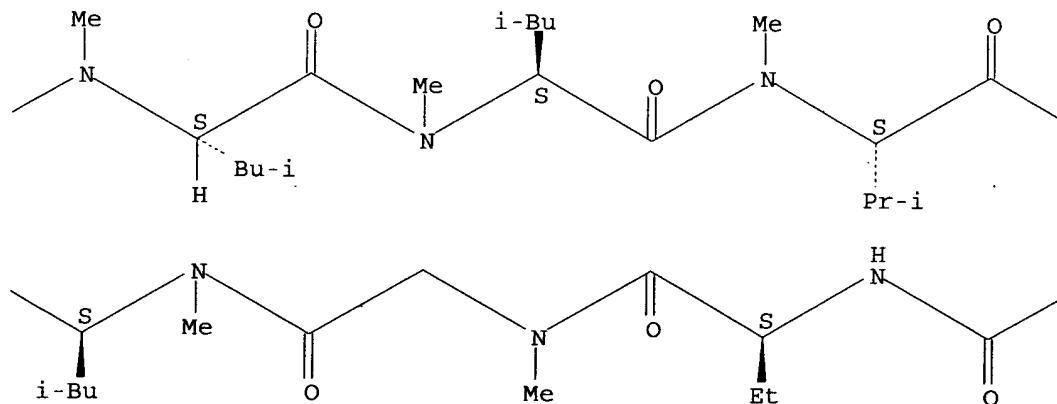
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

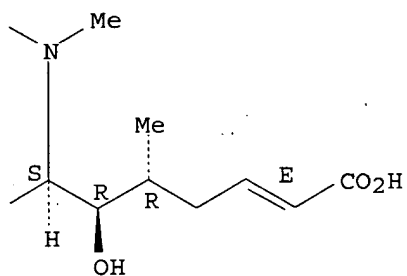
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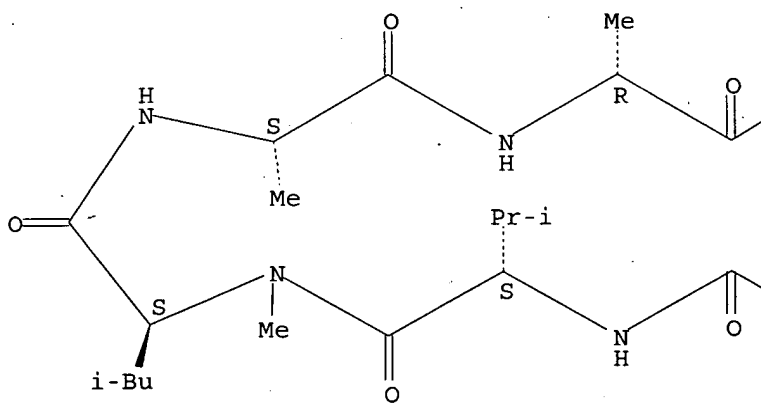


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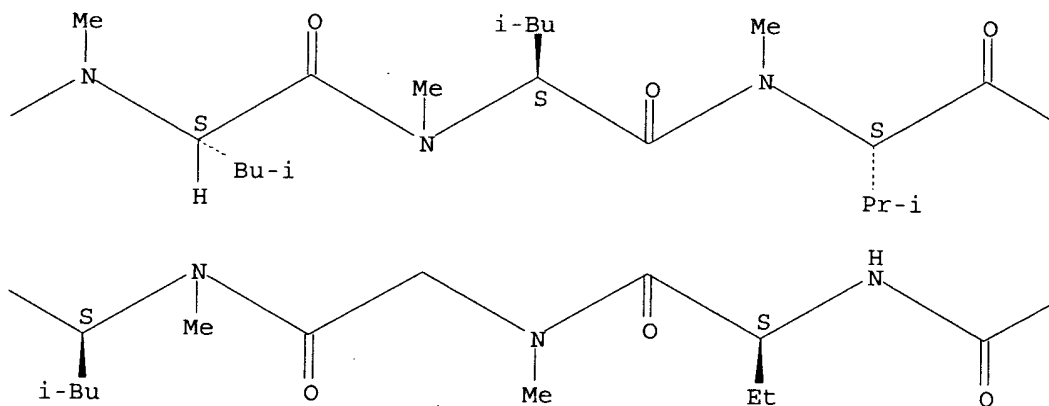
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

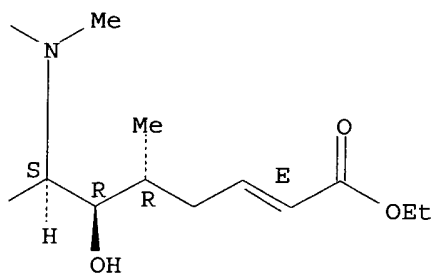
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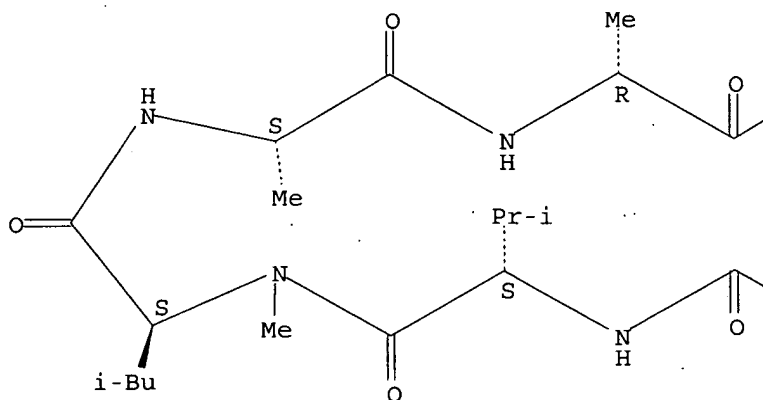


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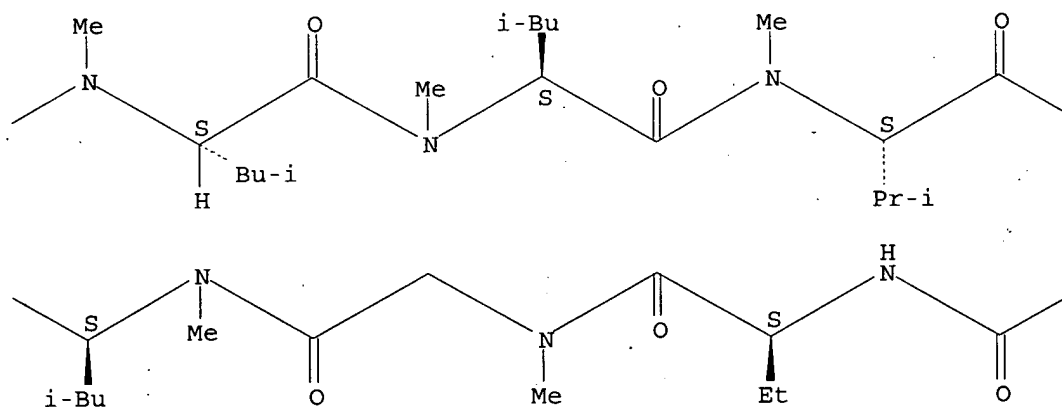
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Absolute stereochemistry.
Double bond geometry as shown.

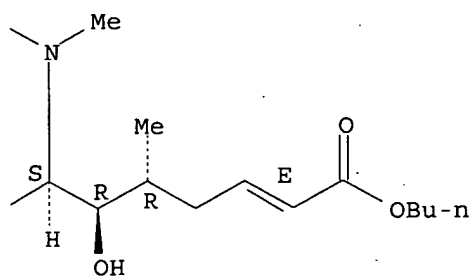
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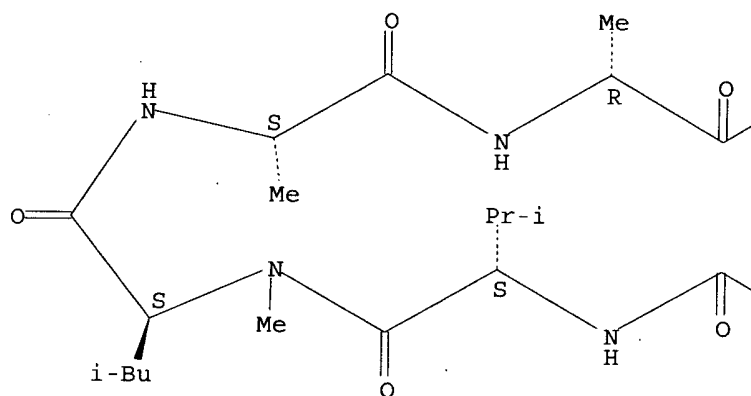


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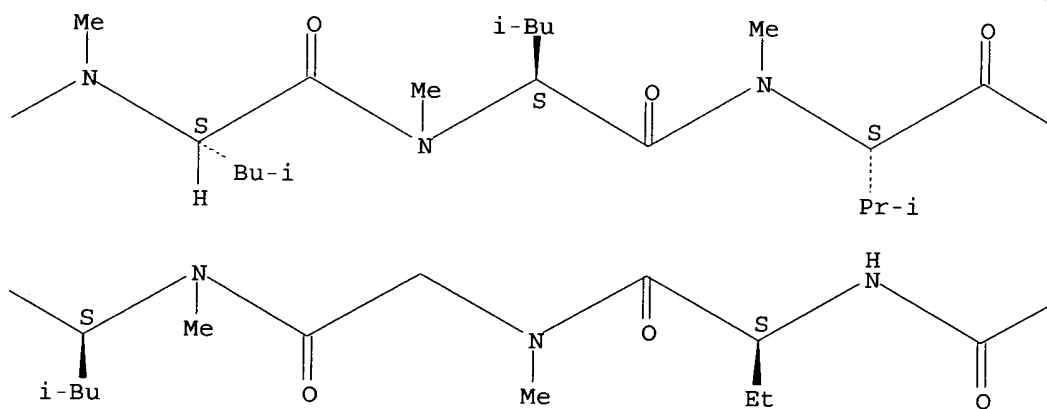
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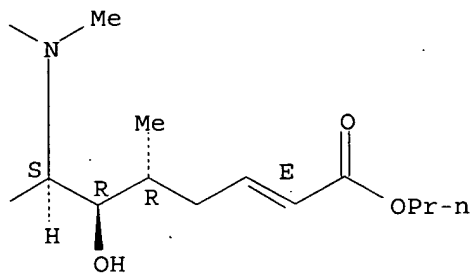
Absolute stereochemistry.
Double bond geometry as shown.

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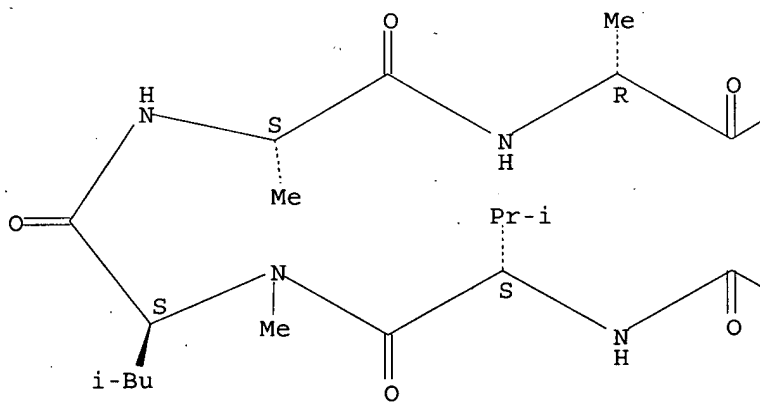




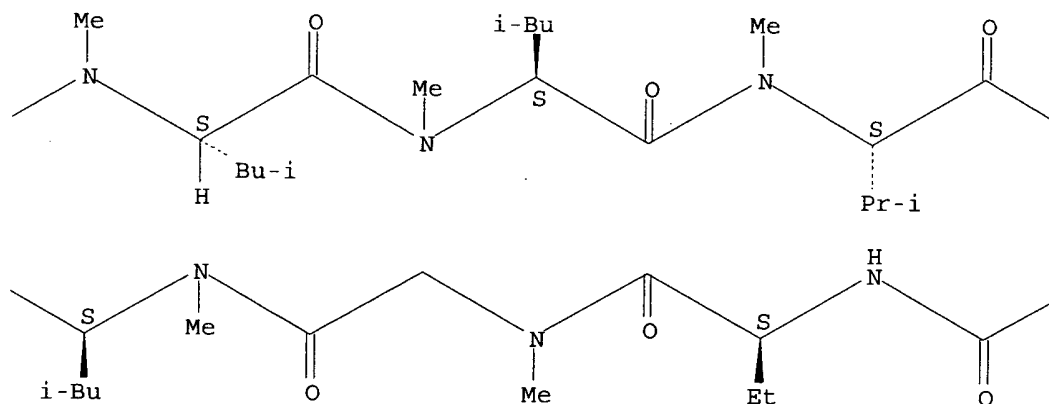
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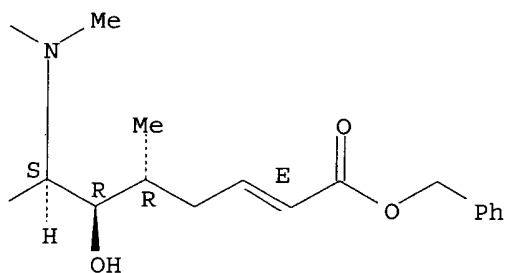
Absolute stereochemistry.
Double bond geometry as shown.



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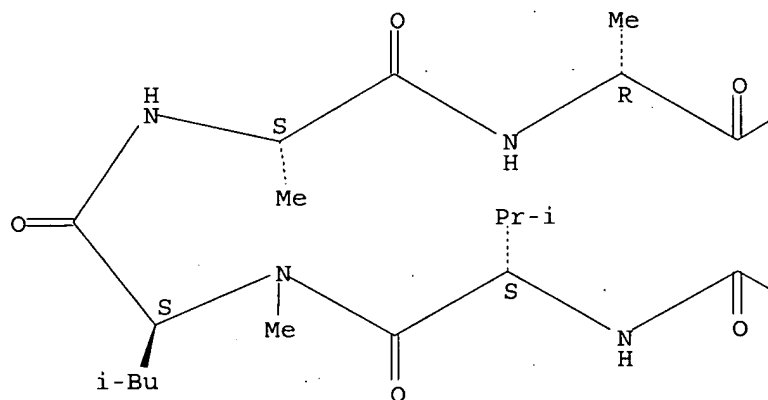


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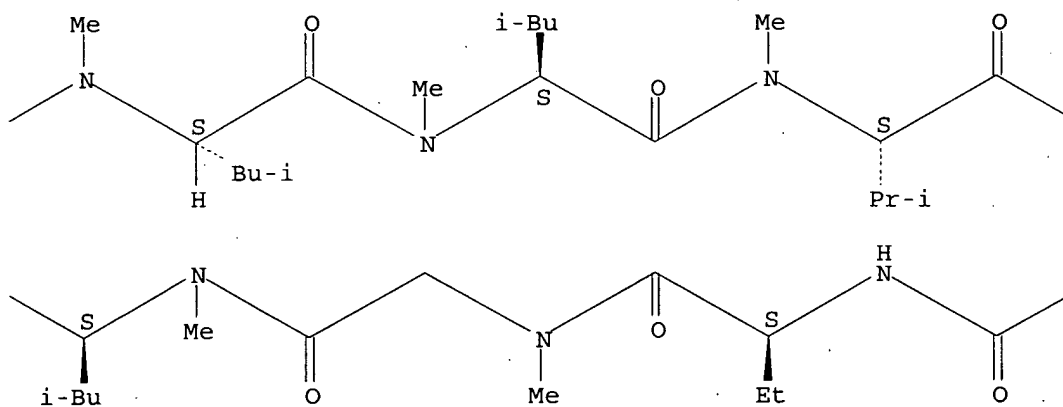
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Absolute stereochemistry.
Double bond geometry as shown.

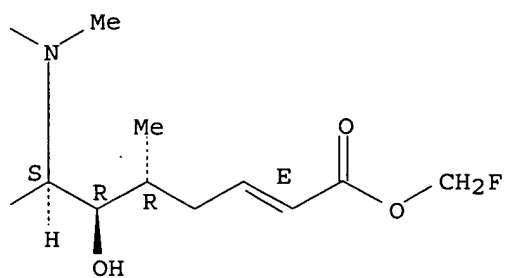
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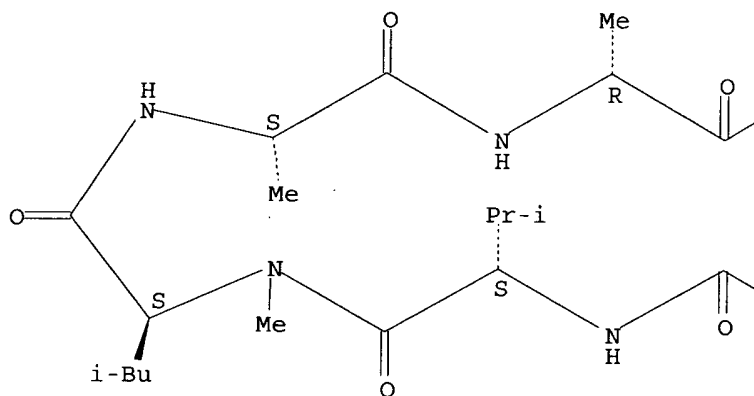


RN 457613-03-5 HCAPLUS

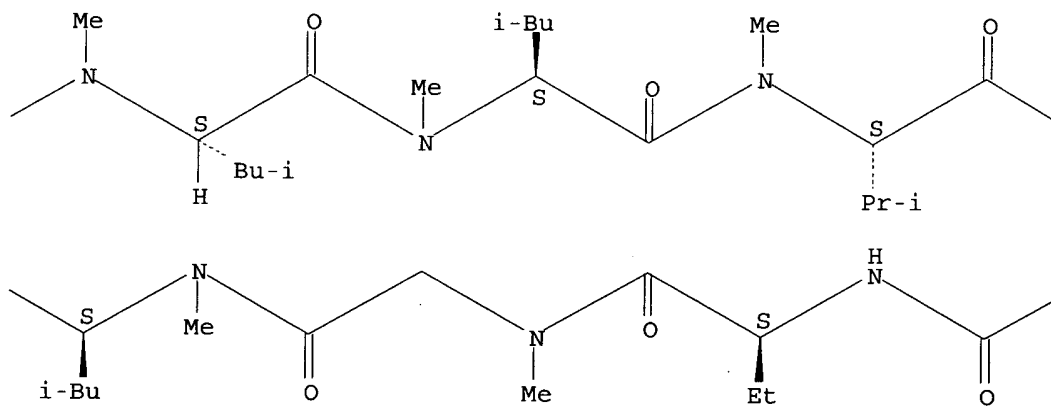
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, difluoromethyl ester (9CI) (CA INDEX NAME)

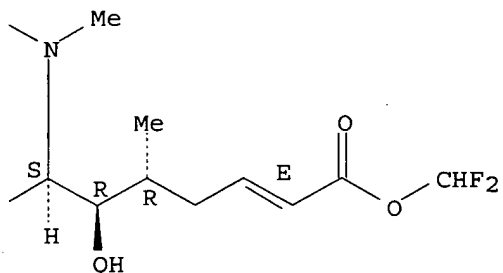
Absolute stereochemistry.
Double bond geometry as shown.

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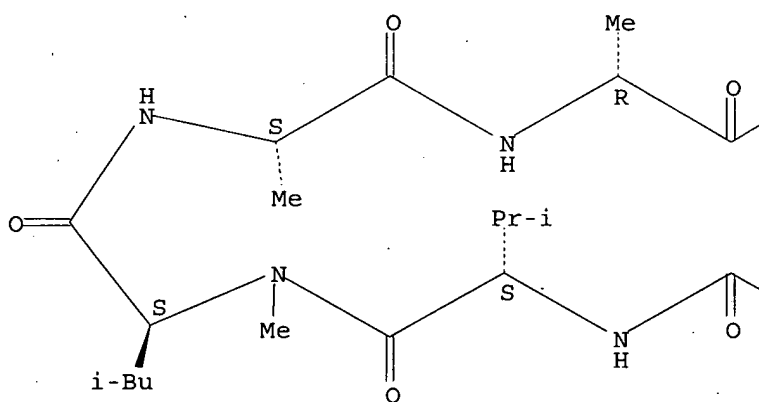




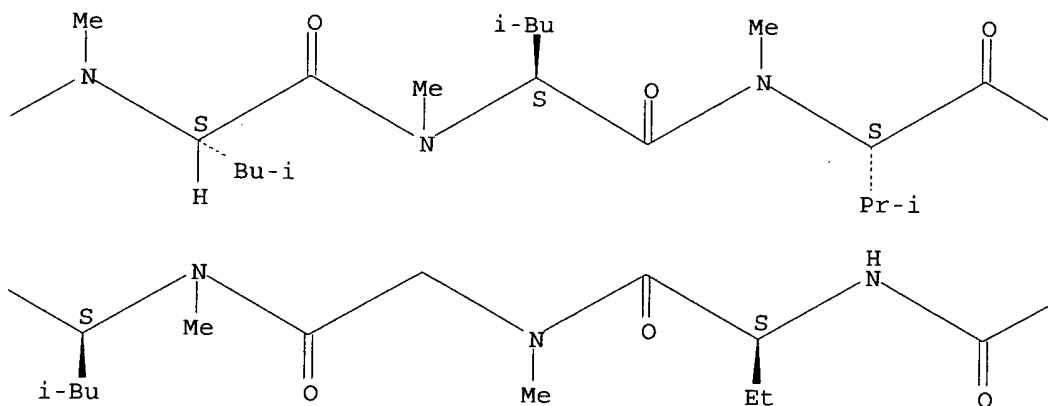
RN 457613-04-6 HCAPLUS

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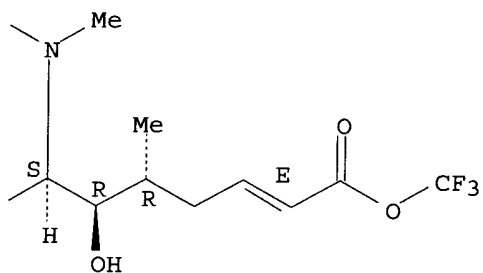
Absolute stereochemistry.
Double bond geometry as shown.



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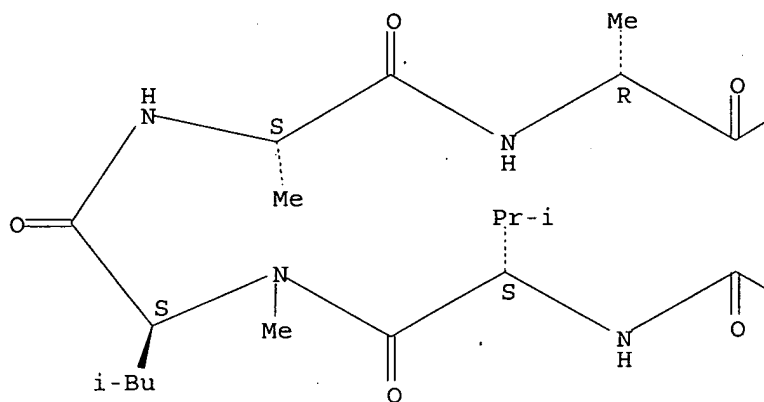


RN 457613-05-7 HCAPLUS

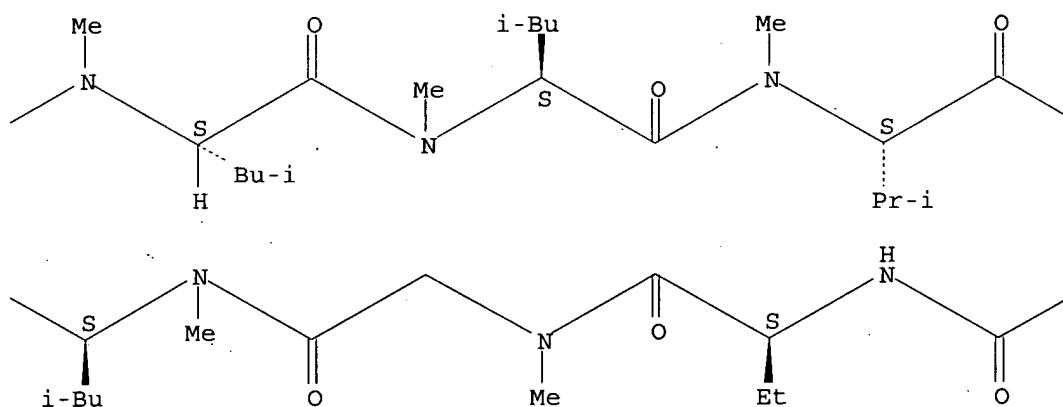
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, 2,2,2-trifluoroethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

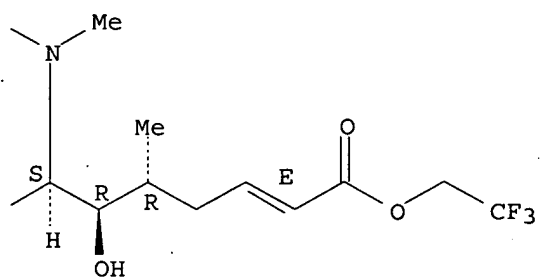
PAGE 1-A



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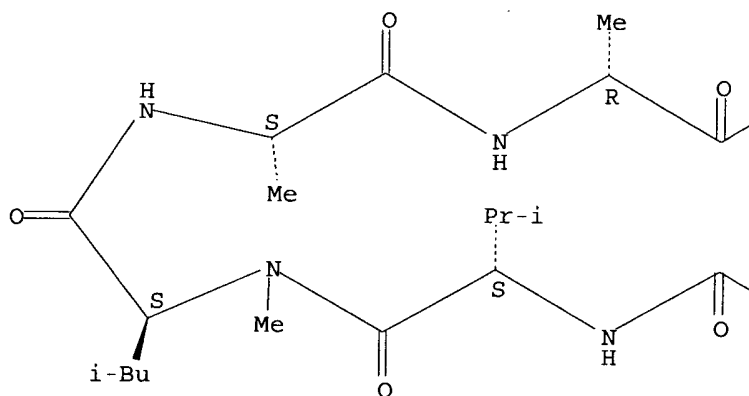


RN 457613-06-8 HCAPLUS

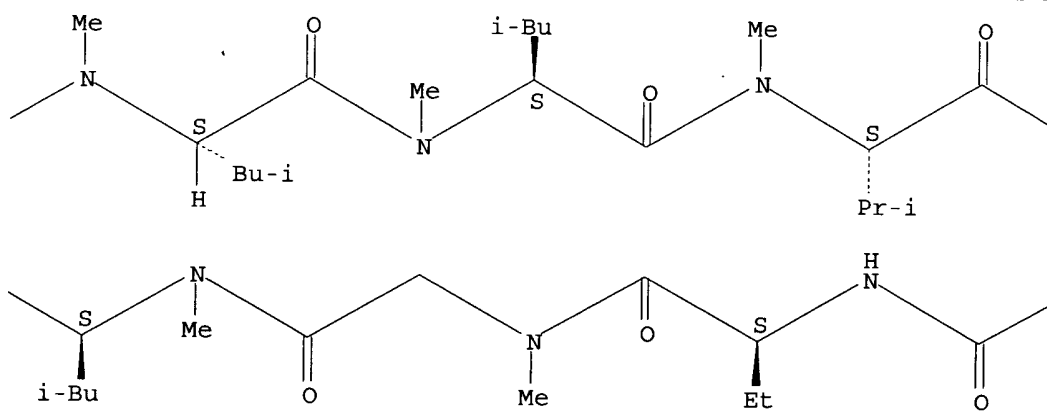
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, chloromethyl ester (9CI) (CA INDEX NAME)

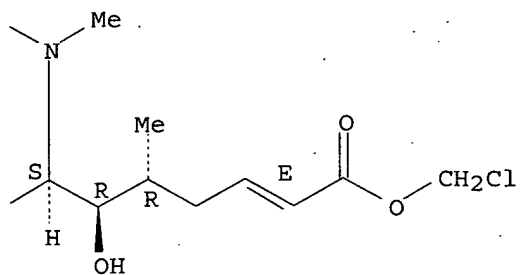
Absolute stereochemistry.
Double bond geometry as shown.

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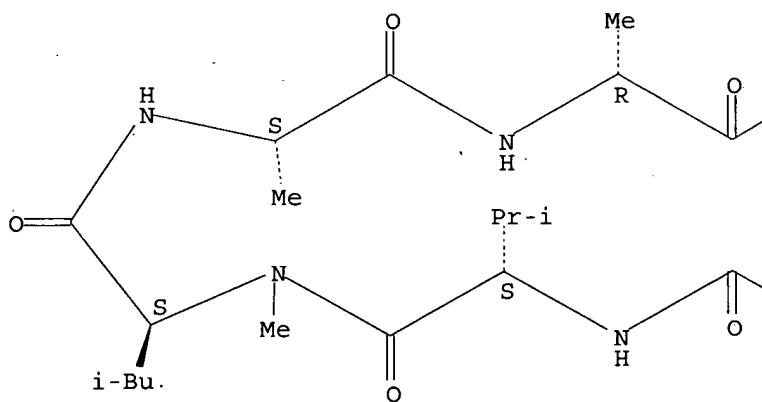


RN 457613-07-9 HCAPLUS

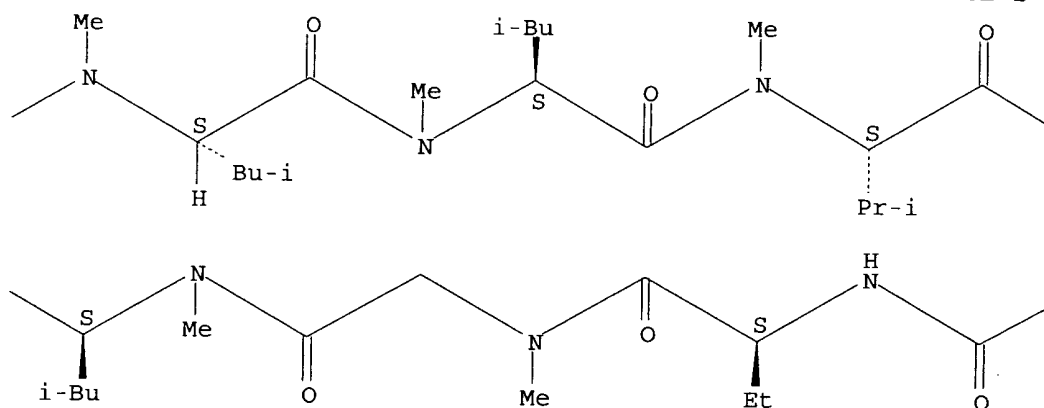
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methoxymethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

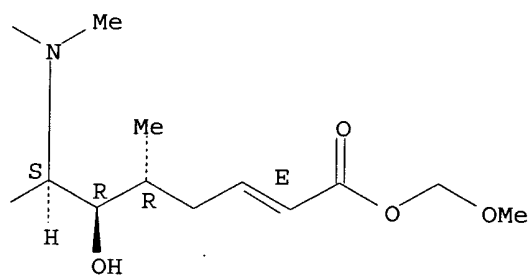
Double bond geometry as shown.



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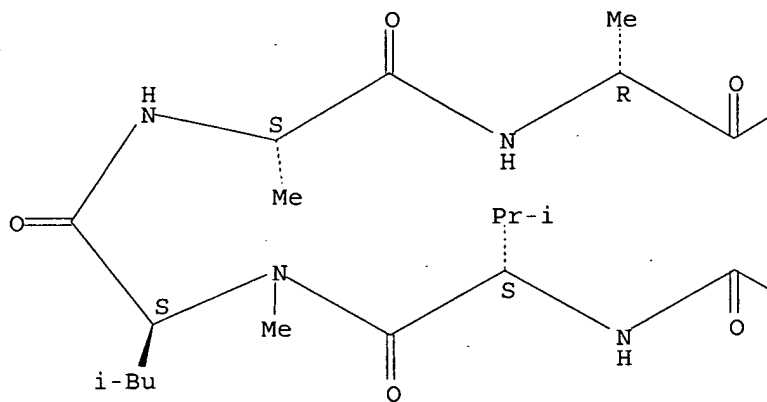


RN 457613-08-0 HCAPLUS

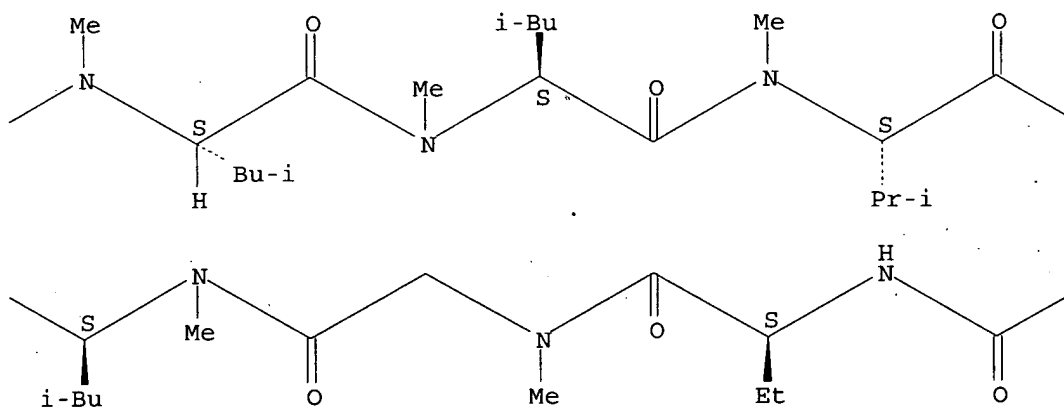
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, (2-methoxyethoxy)methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

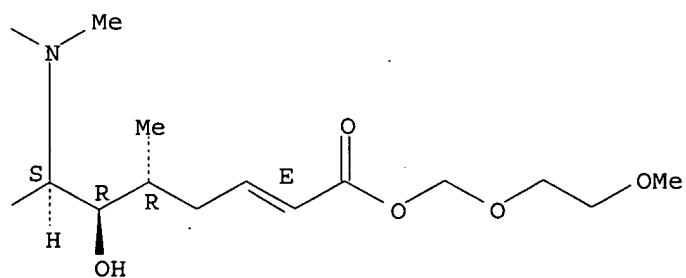
PAGE 1-A



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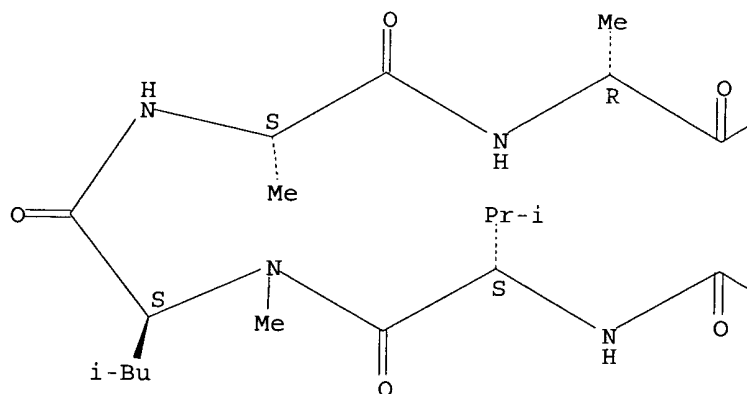


RN 457613-09-1 HCAPLUS

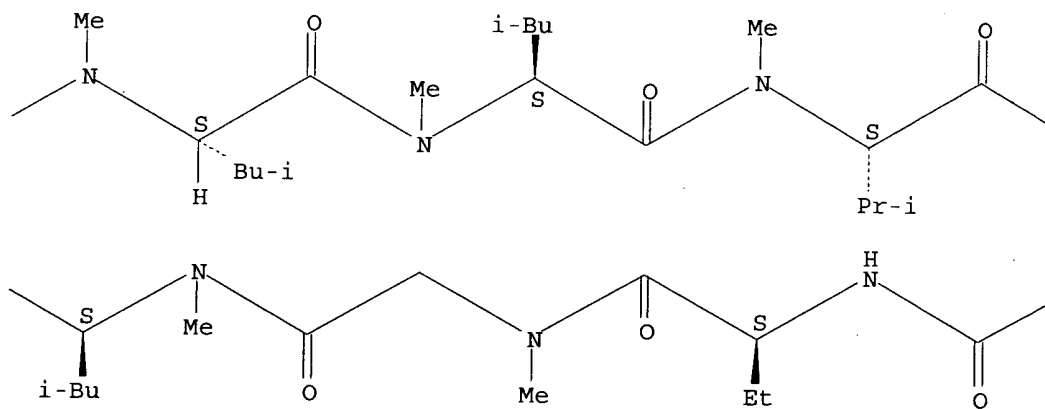
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-8-oxo-8-
[(phenylmethyl)thio]-6-octenoic acid]- (9CI) (CA INDEX NAME)

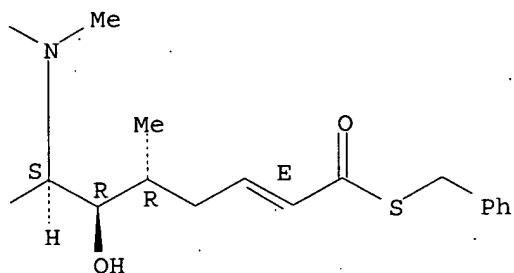
Absolute stereochemistry.
Double bond geometry as shown.

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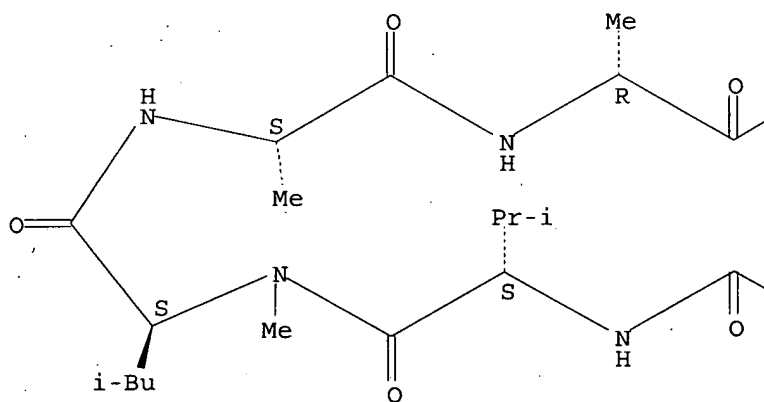




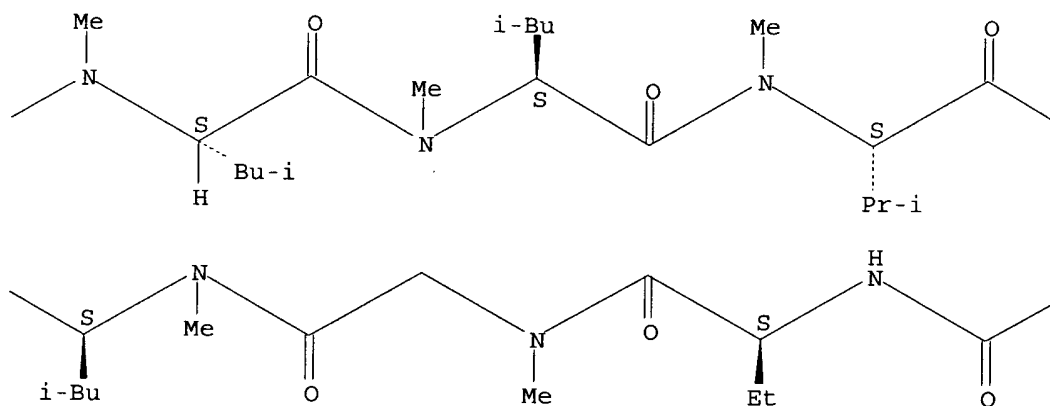
RN 457613-10-4 HCAPLUS

CN Cyclosporin A, 6-[(5E,8R,9R,10S)-9-hydroxy-8-methyl-10-(methylamino)-5-undecenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

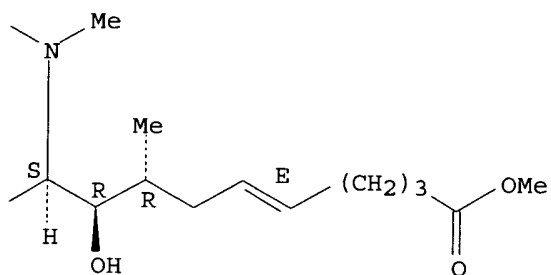
Absolute stereochemistry.
Double bond geometry as shown.



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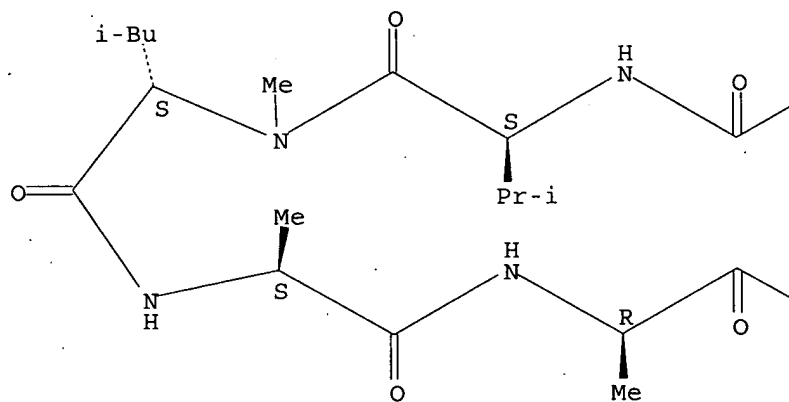


RN 457613-11-5 HCAPLUS

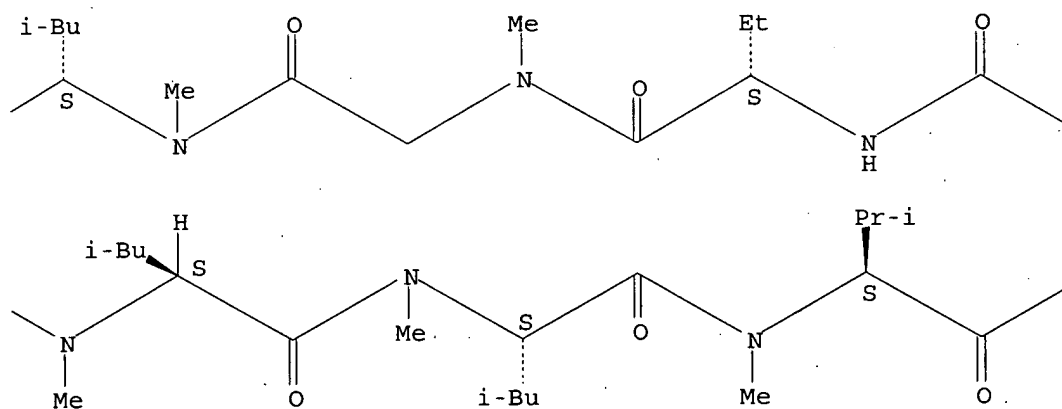
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

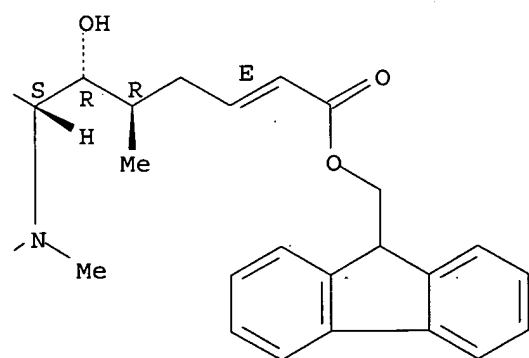
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IT 122547-85-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

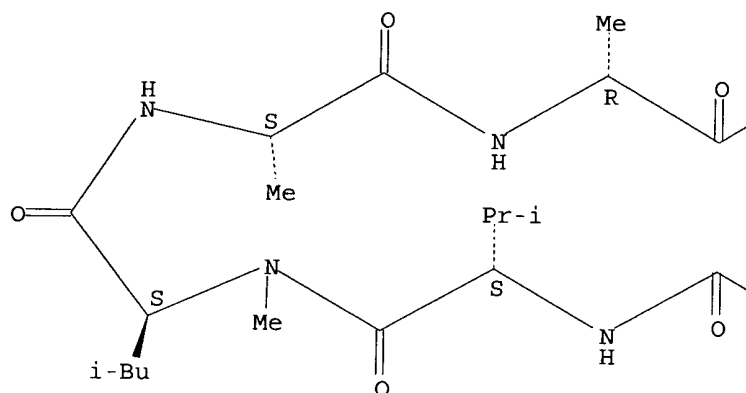
(cyclosporins for the treatment of respiratory diseases)

RN 122547-85-7 HCAPLUS

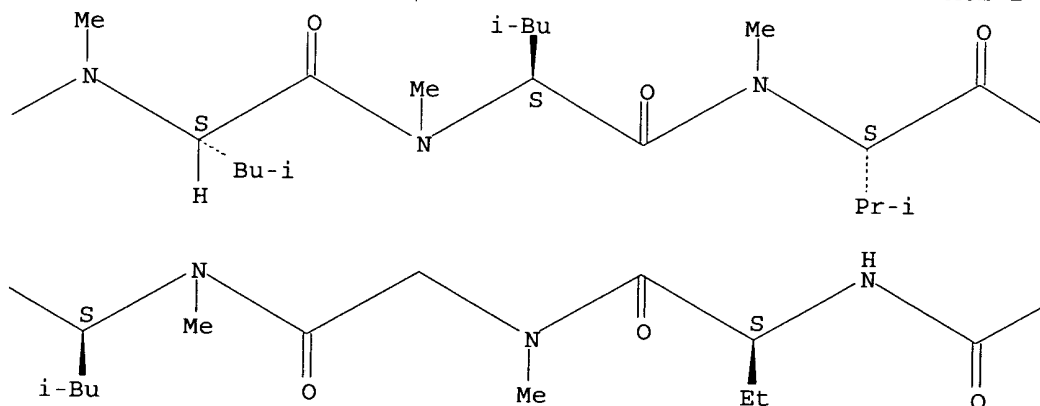
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

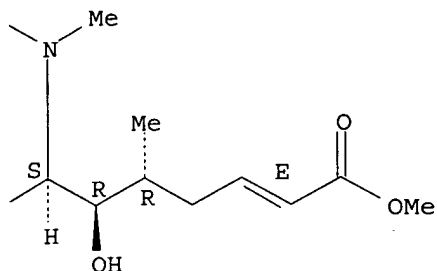
Absolute stereochemistry.
Double bond geometry as shown.

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IT 59865-13-3, Cyclosporin A

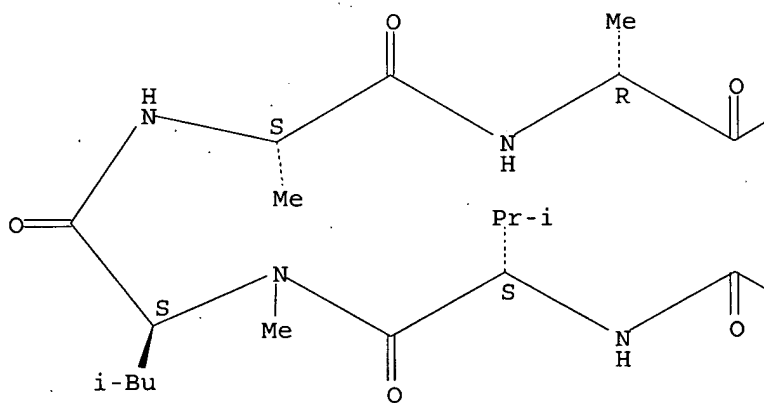
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)

(cyclosporins for the treatment of respiratory diseases)

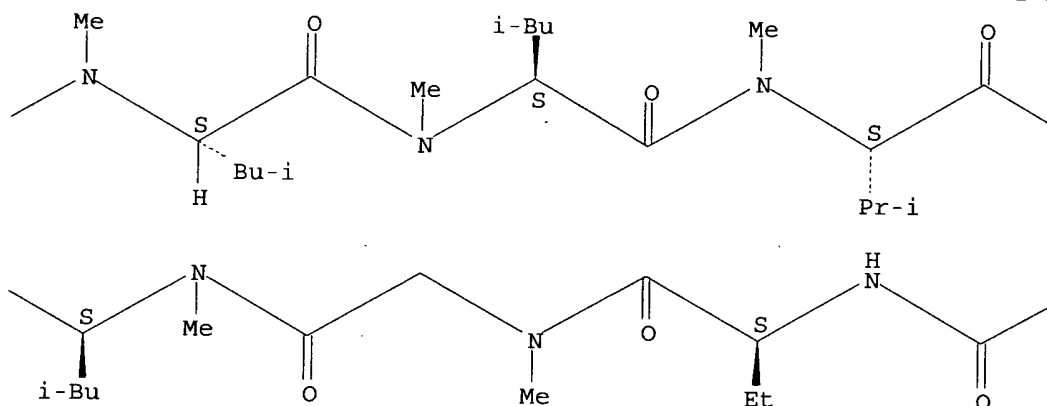
RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

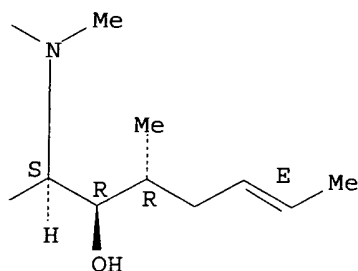
Absolute stereochemistry.
Double bond geometry as shown.



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L17 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:618177 HCAPLUS

TITLE: Synthesis and biological evaluation of novel
Cyclosporin A soft drug derivatives with
potential usefulness in treating asthmaAUTHOR(S): Lazarova, Tsvetelina I.; Hamann, Blake; Chen, Jason
S.; Kang, Jane M.; Homuth-Trombino, Daniela; Hoffmann,
Ethan; McClure, Chris; Eckstein, Jens; Or, Yat
SunCORPORATE SOURCE: Medicinal Chemistry, ENANTA Pharmaceuticals, Inc,
Watertown, MA, 02472, USASOURCE: Abstracts of Papers, 224th ACS National Meeting,
Boston, MA, United States, August 18-22, 2002 (2002),
MEDI-326. American Chemical Society: Washington, D.
C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Short-term inhaled **Cyclosporin A** (CsA) is well tolerated in
humans, but its chronic clin. administration is limited by its toxicity.
A novel approach to circumvent the mechanism-based toxicity of

Cyclosporin A is to develop topical soft drug derivs., which can be administered by inhalation and are subsequently enzymically biotransformed, yielding inactive metabolites. Towards this goal, we have synthesized a series of novel CsA ester analogs using a cross metathesis reaction of CsA and maleate esters. The CsA soft drug analogs show inhibitory activity in a Calcineurin assay with IC50s approx. 2-3-fold greater than CsA, whereas their primary in vitro metabolite is inactive. The synthesis, characterization and biol. evaluation of the CsA soft drug derivs. will be presented.

L17 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:713958 HCAPLUS

DOCUMENT NUMBER: 130:89953

TITLE: Discovery of ascomycin analogs with potent topical but weak systemic activity for treatment of inflammatory skin diseases

AUTHOR(S): Mollison, Karl W.; Fey, Thomas A.; Gauvin, Donna M.; Sheets, Michael P.; Smith, Morey L.; Pong, Melissa; Krause, Ruth; Miller, Loan; Or, Yat Sun; Kawai, Megumi; Wagner, Rolf; Wiedeman, Paul E.; Clark, Richard F.; Gunawardana, Indrani W. K.; Rhoades, Tereasa A.; Henry, Cynthia L.; Tu, Noah P.; Bamaung, Nwe Y.; Kopecka, Hana; Liu, Luping; Xie, Qinghua; Lane, Benjamin C.; Trevillyan, James M.; Marsh, Kennan; Carter, George W.; Chen, Yung-Wu; Hsieh, Gin C.; Luly, Jay R.

CORPORATE SOURCE: Immunological Disease Research, Abbot Laboratories, Abbott Park, IL, USA

SOURCE: Current Pharmaceutical Design (1998), 4(5), 367-379
CODEN: CPDEFP; ISSN: 1381-6128

PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 100 refs. Drug therapy for the major inflammatory skin diseases, which include atopic dermatitis, psoriasis and allergic contact dermatitis, is often inadequate due to poor efficacy, toxicity, or both. Much research has focused on the macrolactam T cell inhibitors as a promising new class of agents for immunotherapy, and medicinal chemical efforts to design novel ascomycin analogs have produced clin. promising agents. A synthetic program to modify the ascomycin nucleus to alter its physicochem. properties and promote systemic clearance is described. A biol. screening strategy to identify analogs with reduced systemic activity and rapid pharmacokinetic elimination led to identification of the clin. candidate, ACTT-281. A swine contact hypersensitivity model was used as a stringent indicator of skin penetration as human doses of topical corticosteroids produced inhibition only in the 50% range and ED50 values were 100-fold less potent than in rat. Also, **cyclosporine** was confirmed to be topically inactive in swine, as seen in human. ABT-281 had topical potency equal to tacrolimus (FK506) despite a severalfold lower potency for inhibiting swine T cells in vitro, consistent with superior skin penetration. ABT-281 was found to have a shorter duration of action after i.v. dosing in monkeys using an ex vivo whole blood IL-2 production assay. Systemic potency was reduced by 30-fold or more in rate popliteal lymph node hyperplasia and contact hypersensitivity assays. Following i.v. or i.p. administration in the swine contact hypersensitivity model, ABT-281 was 19- and 61-fold less potent, resp., than FK506. Pharmacokinetic studies showed that ABT-281 had a shorter half life and higher rate of clearance than FK506 in all three species. The potent topical activity and reduced systemic exposure of ABT-281 may thus provide both efficacy and a greater margin of safety for topical

therapy of skin diseases.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L17 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1997:161979 HCAPLUS
 TITLE: Discovery of ascomycin-derived immunosuppressant A-86281. A novel agent with potent topical but weak systemic activity.
 AUTHOR(S): Luly, Jay R.; Or, Yat Sun; Kawai, Megumi; Wagner, Rolf; Wiedeman, Paul E.; Clark, Richard; Gunawardana, Indrani; Kopecka, Hana; Rhoades, Teresa; et al.
 CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
 SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-147. American Chemical Society: Washington, D. C.
 CODEN: 64AOAA
 DOCUMENT TYPE: Conference; Meeting Abstract
 LANGUAGE: English

AB The immunosuppressant tacrolimus (FK506), an ascomycin analog, shares with **cyclosporine** a similar mechanism of action, good oral efficacy in transplantation and inflammatory/autoimmune diseases, and, unfortunately, similar major toxicities. In an effort to minimize potential side effects of this class, we synthesized several series of ascomycin analogs to identify compds. with potent topical immunosuppressive activity, but less systemic immunosuppression following absorption. In vitro, A-86281 (ABT-281) potently inhibits T cell activation, and in vivo shows topical potency comparable to FK506 (ED50's 0.9% and 0.6%, resp.) in a swine contact hypersensitivity model. In contrast, A-86281 displays a more rapid disappearance from the circulation, and is a markedly weaker systemic immunosuppressant in multiple animal models. The A-86281 profile of potent topical but weak systemic activity should be advantageous for minimizing systemic immunosuppression and consequently the mechanistically-related toxicities associated with immunophilin-dependent immunosuppressants.

L17 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1993:204871 HCAPLUS
 DOCUMENT NUMBER: 118:204871
 TITLE: Evaluation of calcineurin's role in the immunosuppressive activity of FK 506, related macrolactams, and **cyclosporine**
 AUTHOR(S): Lane, B. C.; Miller, L. N.; Kawai, M.; Or, Y. S.; Wiedeman, P.; Holzman, T. F.; Luly, J. R.
 CORPORATE SOURCE: Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, USA
 SOURCE: Transplantation Proceedings (1993), 25(1, Book 1), 644-6
 CODEN: TRPPA8; ISSN: 0041-1345
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Calcineurin, a Ca²⁺/calmodulin-activated phosphatase, was studied as a possible target for the immunosuppressive activities of FK-506 and **cyclosporin A** associated with their resp. immunophilins, FK-506-binding protein and cyclophilin. The mixed leukocyte responses and calcineurin phosphatase activity under exposure to the drugs were determined. The phosphatase is a plausible target.
 IT 59865-13-3, **Cyclosporin A**

RL: BIOL (Biological study)

(immunosuppression from, calcineurin phosphatase in mechanism of)

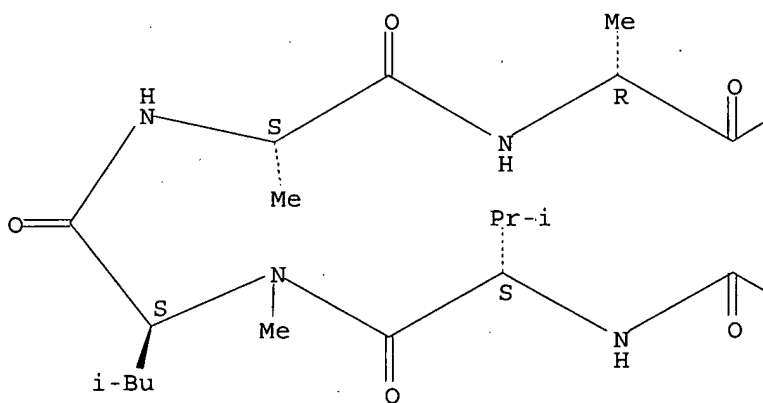
RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

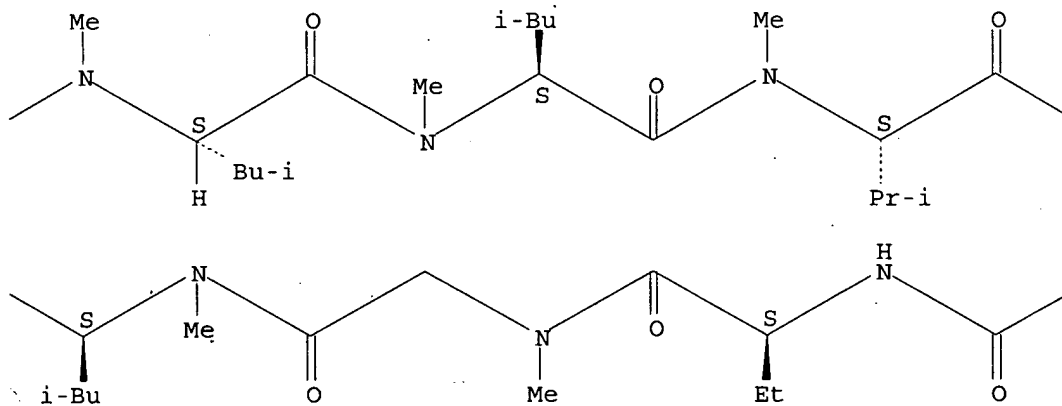
Absolute stereochemistry.

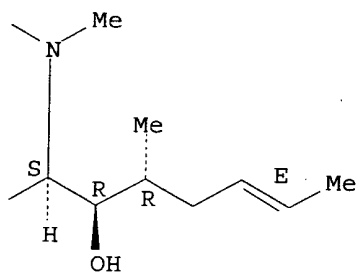
Double bond geometry as shown.

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